Circulation

JANUARY 1961
VOL. XXIII NO. 1

AN OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Stephen Hales, September 17, 1677-January 4, 1761

IN THIS YEAR a proper pilgrimage might be made to St. Mary's Church in Greater London, beneath the tower of which in 1761 the mortal remains of one Stephen Hales were interred. At that time the church was in the village of Teddington situated on the north bank of the Thames about 12 miles from the city of London. The small red-brick church with low square tower sits well back from a garden wall and behind lies the expected burial ground. The church has a simple interior and the original stained-glass windows, destroyed by the bombing in the war years 1939-1945, have been for the most part replaced by plain glass. There is a large church across the street serving the parish, but the old church is apparently still favored by many of the older "Low Church" group for their services. The original stone marking the place of interment has been moved from the floor to the left wall of the tower wall, but the inscription is still quite clear.

A young cardiologist, who might visit the church with just his meager knowledge of Hales' contribution to the measurement of blood pressure by a vertical tube attached in an artery of a horse, all gained as passing comments at his medical school, should not be surprised if he found persons of many other disciplines already at the shrine. Among the congregated group there might be botanists, plant physiologists, pulmonary and peripheral vascular physiologists, hygienists, neurologists, orthopedists, air-conditioning engineers, and historians of the State of Georgia.

The Reverend Stephen Hales, D.D., F.R.S.

A certain slant of this communication for the American reader is acknowledged, and to give a time setting for Hales' life, it may be helpful to point out that he lived just before the American Revolution; George III, so well

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publicized in American history, ascended the throne just a year before Hales' death. This temporal relationship has greater force when it is known that the "old philosopher," Hales, had been among the men suggested as a tutor for the young prince, at 13 years of age, when his father, the Prince of Wales, died in 1751.

In a larger historic setting relating to the progress of knowledge of the circulation and respiration, it is strikingly pertinent that this bicentenary of Hales' death is so close to the tercentenary of Harvey's death (1657). It is interesting that the birth years were just a year short of being a century apart, and that both men lived to be very old men. While one might designate Harvey's experiments and deductions *hydraulics,* Hales' contributions, self-styled *hydrostatics* (and *hematostatics*), are well named indeed, further defining as they did the pressures forcing the blood to flow along the circulatory pathway Harvey had demonstrated so well. There are two basic references for the tyro medical historian who has become interested in Hales, namely, the book written by the man himself, relating to blood pressure and flow, his *Statical Essays* . . . ,[1] published in 1733*, and second, the impressively thorough biography prepared by Clark-Kennedy[2] and published in 1929. This biography sprang from the oration given by Clark-Kennedy in 1927, on the occasion of the two hundred and fiftieth anniversary of the birth of Hales, celebrated by Corpus Christi College, Cambridge (where Hales had been admitted as a Fellow in 1703).

In the present era of rapid publication it is germane to remark that the full publication of Hales' work on blood pressure was delayed 20 years, although in essence the work had the equivalent of abstract publication with its contemporary reporting to the Royal Society. Parenthetically, in whimsy, it may be noted that botanical experiments preceded by 2 years, and continued and seemingly dominated, his scientific efforts through the short period of his marriage, so that his wife apparently did not have to endure any stress of the large animal experimentation, in the vicinity of the parsonage, which had taken place about 20 years previously. Hales was a bachelor to the age of 43 years and a widower from 44 years of age. Alexander Pope (known well for the quotation, "The proper study of mankind is man"), a forthright spokesman against cruelty to animals, and friendly although critical of Hales' experiments, became a neighbor in 1719, which was, as mentioned, at a time when Hales' energies were largely bent toward his "Vegetable Statics" works. In the eighteenth century cruelty to animals was rampant, but whether this general atmosphere or Descartes' mechanistic philosophy (stating that animals, having no soul, had no pain) of the previous century favored the implementation of Hales' works, is conjectural.

It is a duty to dispel any notion that Hales was an itinerant scientific amateur with a mediocre education, which is sometimes implied from the fact that he was a long-time village parson. Already at Cambridge he was known to be avidly interested in science, and one lifelong friendship established there was with a William Stukeley, a physician, who established in Cambridge one of the first animal-experimental laboratories. One of the results of this association was a reproduction of the bronchial tree in the form of an anatomic cast in lead; that is, after "rotting off the substance of them [lungs] with water I had the finest animal plant that ever was seen, which was mightily admired." While he was at Cambridge his interests were multiple, and included the repetition of Boyle's experiments in physics and the construction of a teaching model to illustrate the movement of the planets.

The Reverend Hales first attended a meeting of the Royal Society when he was 40 years of age (1717), was proposed for membership about a year later at a meeting, chaired by Sir Isaac Newton, and was admitted later in that year.

Cardiovascular Physiologist

It is perhaps regrettable that the work of Hales, as presented to many medical students,

*The second edition, published in 1740, was the one available for study by the author.

is epitomized by the pressure measurement by a vertical tube, an experiment which in itself does little to reflect the sophistication and elegance of his experimental work for his time, or the depth of the basic concepts with which his inquiring mind dwelt. He had good understanding of hemodynamics—the relationship of pressure to flow and to resistance. He embarked upon a program to define the two factors related to pressure, namely, the cardiac output and the peripheral resistance, having first established the mean values of the arterial and venous pressures by the level of the column of blood supported in a glass tube connected either to the end or side of the vessel.

The cardiac output he estimated from the volume of wax casts of the ventricle, multiplied by the pulse rate. He described the hemodynamic profile of different animals, such as the pulse rate, cardiac output, stroke volume and systemic pressure in the ox, horse, sheep, and dog. He gave a clear explanation of how the intermittent flow in the aorta is "carried on in the finer capillaries, with an almost even tenor of velocity" by means of the distensibility of the arteries. He showed that the cross-sectional area of the two branches beyond a bifurcation of an artery is always greater than that of the parent artery, and logically concluded that as the vascular volume increases toward the periphery, the forward velocity will decrease. Realizing that there must be a zone of resistance, despite the general increasing vascular area as one approaches the periphery, he attacked the problem by an experiment which, despite its faults by modern standards and probably unrecognized assumptions, impresses one as a more beautiful example of the experimental method than his measurement of blood pressure. He perfused the distal aorta, allowing the perfusate to escape through a longitudinal cut in the intestine; he determined the flow rate, then sequentially cut the mesentery close to the bowel and then near the aorta, redetermining the flow at each step, establishing the main site of peripheral resistance in the tiny arteries or capillaries. He also found that warm water increases the flow; cold water and various drugs decrease it. (In his report we read, "Hence we see that brandy contracts the fine capillary arteries of the guts.") The direct measurement of pressure in the pulmonary artery was beyond the scope of his experimental technics, but he reasoned that the force (pressure) required to force the blood out of the right ventricle is less than that of the left; *videlicet*, "so may observe, that the substance of the right ventricle has not near the thickness of that of the left."

It is of incidental interest that he measured the force required to burst arteries and veins, in relation to the fact that King George II, to whom his book was dedicated, died of a ruptured heart.

Respiratory Physiologist

Reference already has been made to Hales' suggestion to Stukeley of making a metal cast of the tracheobronchial tree. Hales continued his interest in pulmonary compartments and made measurements of pulmonary volumes by blowing lungs up under water and measuring the fluid displaced. He calculated the alveolar surface area, the alveolar capillary surface area, the volume of blood in the pulmonary capillaries, and the relative velocity of blood within them.

His role in discovering carbon dioxide deserves an extensive critique, but the fact that he did such early work on the gas cannot be denied, although he did not clearly understand his discovery. He experienced personally the effects of rebreathing and suggested the use of protective respirators for workers exposed to noxious fumes.

Ventilation

It was in the design and installation of ventilators in ships, hospitals, and jails that Hales felt he had made his greatest contributions to mankind, and his later years were devoted largely to the furtherance of widespread adoption of his ventilators. These were large bellows, ordinarily operated manually, but sometimes by windmills, the latter being exemplified by the contemporary pictures of the infamous Newgate prison. No doubt there was a change in the death rate in jails and hos-

pitals after the installation of the ventilators, but other hygienic measures seemingly were instituted simultaneously. It is an interesting, although idle, speculation that his primitive air conditioning, associated with a reduction in the death rate from typhus, may have anticipated by 200 years the accomplishments of modern, although somewhat makeshift, air conditioning in the treatment of scrub typhus fever in hospitals of the Burma theater in the second world war.

The testimonial letters to Hales from ship captains extolling the value of the ventilators in slave ships and émigré ships are very convincing, and so it is that not a few American citizens may owe their "being" to the fact that Hales' ventilators saved the lives of their ancestors.

Prohibitionist

Hales was an ardent prohibitionist, and declared he would sooner have rid the world of the evil of drunkenness than to have accomplished anything else. He wrote two anonymous tracts entitled "A Friendly Admonition to the Drinkers of Brandy and Other Distilled Spirituous Liquors" (1734) and "Distilled Spirituous Liquors, the Bane of the Nation" (1736). These must be interpreted in the light of the times, the London of Hogarth's "Gin Lane" and of the abortive gin acts and riots. One might facetiously claim that Hales had anticipated space travel, for in an exhortation against the exportation of "Spirits" in a letter written shortly before his death he says "Could we export these mighty destroyers to the inhabitants of the moon, or of Saturn's Satellites, I would be zealously and utterly against it . . ." One might wonder whether Hales' pamphlets could have had any influence on Benjamin Rush, who loudly proclaimed the evil of drink in America and who was a resident in London at Benjamin Franklin's home just 6 years after Hales' death. (Rush's *Enquiry Into the Effects of Ardent Spirits Upon the Human Body and Mind* was not published until 1812.)

Trustee of the Georgia Colony

Georgia, the last of the English colonies to be founded in America, was named for George II, and began as a private philanthropic enterprise, supported by Parliament as a bulwark to the south of the Carolinas against Spanish aggressive threats. It was planned to give new opportunity to debtors, the poor, and the English and continental religious minorities. Of particular interest were the initial regulations against slavery and the sale of rum, which, however, seemed to have been promulgated as much for business as for moral reasons. Hales was one of the Charter Trustees (1732) of the colony and remained a very active member until the colony was transferred to governmental jurisdiction, 21 years later. He is given credit for the choice of the Wesley brothers as replacement ministers in the colony in 1735, and in this choice it is assumed he was influenced by their missionary zeal, interest in medical care, and perhaps their antispirits (and anti-rum) convictions. Personal difficulties developed while John Wesley was in Georgia and necessitated his return to England. He remained a friend, and his comment concerning Hales, toward the end of the latter's life, "How well do philosophy and religion agree in a man of sound understanding," is quoted as an ending to a number of eulogies to Hales.

Hales drew up his will in 1759, and amongst the items appears this bequest, "All my bound books at Teddington . . . I give and bequeath for a public parochial library to such Town or Parish in Georgia in America, the Governor shall think fit to appoint."

There is no record that this library was transferred to the Georgia colony that I have been able to discover.[3, 4]

Plant Physiologist

The avid curiosity, conceptual thinking, and ingenuity of experimental design are abundantly portrayed in Hales' reports concerning the factors determining the flow of sap in trees and vines, the sap pressure in the spring of the year, and the transpiration of moisture from leaves. He demonstrated the differential zones of growth in twigs and leaves by methods that are still used. The shortness of this paragraph should not indicate that his contributions to botany were of

less eminence than his work in biology but, rather, that the present communication is directed toward Hales' influence in the development of animal physiology.

Other Medical Contacts

As a recognized scientist Hales on occasion was called upon to serve as a referee in the evaluation of various nostrums and patent medicines. He showed care and charity in his investigations, but his interpretations were less critically couched than his physiologic work. Curiously, he received the Copley Medal of the Royal Society (1739) for his investigations on the solubility of urinary calculi, perhaps the least impressive, in retrospect, of his scientific endeavors.

For the orthopedist and bone physiologist Hales' pioneer work on the growth pattern of long bones, demonstrating epiphyseal growth, remains exemplary. For the attention of the neurophysiologist there is no doubt that Hales demonstrated spinal reflexes in the "spinal frog." To the agriculturist it would be interesting to learn that Hales developed a winnowing machine.

For improvement in the powers of survival he recommended frequent wetting of the clothes with water, and this action was said to have been effective in Bligh's open-boat voyage of 1789. He would have contemporary support in his endorsement of exercise as a health measure—in his own words, "many cogent arguments for temperance and exercise do always occur."

At the age of 70 years Hales delivered the Annual Crounian Sermon for the Royal College of Physicians with the title, "The Wisdom and Goodness of God in the Formation of Man," and he found an appropriate text in Job X, 11, 12 beginning, "Thou hast clothed me with skin and flesh and hast fenced me with bones and sinews. . . ."

In conclusion, three comments have been chosen from Hales' contemporaries and a fourth comment from his own pen concerning the way of an investigator. The first is from a fellow minister who manifests little historic perspective (Twining, "The River").

> Green Teddington's serene retreat
> For philosophic studies meet,
> Where the good Pastor Stephen Hales
> Weighed moisture in a pair of scales,
> To lingering death put Mares and Dogs,
> And stripped the Skins from living Frogs.
> Nature, he loved, her Works intent
> To search or sometimes to torment.

The second was written by a politician (letter from Horace Walpole to Sir Horace Mann [1752]) on the occasion of selecting a tutor for George, heir apparent to the throne, "Among the other candidates, they talk of Dr. Hales, the old philosopher, a poor good primitive creature. . . ." Apparently Walpole thought Hales politically "safe"—it is an immediate speculation whether, if the appointment had taken place, any of Hales' espousal of the scientific method and humility could have modified the later behavior of George III in the crisis with the American colonies.

The third comment is from a naturalist, admirer and later curate at Farringdon (Gilbert White), "The last act of benevolence in which I saw him [Hales] employed was at his rectory of Farringdon, . . . much busied in painting white with his own hands the tops of foot path posts, that his neighbors might not be injured in running against them in the dark." (This seems to be allegorically appropriate, for did not Hales also paint the tops of posts, indicating the scientific pathway for his followers, in the pursuit of knowledge through research?)

Finally, we have from his own pen (introduction to Hemostatics): "In natural philosophy we cannot depend on any mere speculations of the mind; we can only with mathematicians reason with any tolerable certainty from proper data, such as arise from the united testimony of many good and creditable experiments.

"If therefore some may be apt to think that I have sometimes far indulged conjecture, in the inferences I have drawn from the events of some experiments, they ought to consider that it is from these kinds of conjectures that fresh discoveries first take their rise, for although some of them may prove

false yet they often lead to further and new discoveries."

Before the medical pilgrim leaves Teddington Church, he may wish, in caprice, to note the tombstone of one Isabel, Countess of Denbigh, abutting the tower. The dowager buried beneath had had a fond affection for Hales and had arranged to be buried as close to him as possible, leading Lord Buckinghamshire to suggest facetiously that she ought to have arranged cremation of both bodies so that the intermingled dust could be mixed with soil on Strawberry Hill, whose pious owner, Walpole, would plant a myrtle thereon. On returning to central London, the pilgrim may wish to visit briefly Westminster Abbey, where on the right wall may be seen (with the help of a curate) a memorial placed there by Augusta, mother of George III, and thence to some bookstore to inquire of, and perhaps to price or buy, *Statical Essays.*

HOWARD B. BURCHELL

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It seems not unreasonable, on the other hand, though not far to indulge, yet to carry our reasonings a little farther than the plain evidence of experiments will warrant; for since at the utmost boundaries of those things which we clearly know, there is a kind of twilight cast from what we know, on the adjoining borders of *Terra incognita,* it seems therefore reasonable in some degree to indulge conjecture there: otherwise we should make but very slow advances in future discoveries, either by experiments or reasoning: for new experiments and discoveries do usually owe their first rise only to lucky guesses and probable conjectures, and even disappointments in these conjectures do often lead to the thing sought for: thus by observing the errors and defects of a first experiment in any researches, we are sometimes carried to such fundamental experiments, as lead to a large series of many other useful experiments and important discoveries.—STEPHEN HALES, B.D., F.R.S. *Haemastatics.* Preface, Vol. II, London, 1733.

Reoperation for Mitral Stenosis

A Discussion of Postoperative Deterioration and Methods of Improving Initial and Secondary Operation

By DWIGHT E. HARKEN, M.D., HARRISON BLACK, M.D., WARREN J. TAYLOR, M.D., WENDELL B. THROWER, M.D., AND LAURENCE B. ELLIS, M.D.

SIGNIFICANT clinical improvement after valvuloplasty for mitral stenosis can be anticipated in 70 per cent of group III patients followed 5 years and 52 per cent of those in group IV[1] Nevertheless, the first 1,000 patients in our series have been followed from 2 to 9 years, and some degree of deterioration after an initially favorable result was found in 228. Critical scrutiny of the factors involved in this deterioration should lead to better selection of patients, to the evolution of better operations, and perhaps to the prevention of "restenosis." In the analysis of the results,[1] 3 factors appeared to be particularly responsible for deterioration: inadequate initial surgical correction (45 per cent); mitral insufficiency preexisting or following operation (22 per cent); and recurrence of rheumatic fever (17 per cent).

Many of these patients have seemed suitable for reoperation. Experience gained at these second operations has not only emphasized the seriousness of an inadequate initial operation but has underlined the difficulties and hazards of the usual method of reoperation. Dissatisfaction with the safety and results of the old method of reoperation prompted the development of the new procedure, presented here. This new technic has been chosen after careful consideration and trial of the right-sided approach as advocated by Neptune and Bailey,[2] open operation as suggested by Kay and Zimmerman,[3] by Lillehei et al.,[4] transventricular valvotomy as proposed by Logan and Turner,[5] Tubbs,[6] Cooley and Stoneburner,[7] and Gerbode,[8] and the transauricular dilator valvotomy suggested by Dubost and Blondeau.[9]

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Supported in part by grants H-2419, H-442, and HTS-5231 from the National Heart Institute, U. S. Public Health Service.

Material

The first 80 reoperations on 79 of our patients are analyzed here. One patient had 2 reoperations. All but 5 were from the first 1,000 above.[1] The operative findings and clinical observations have been analyzed in order to reconstruct as accurately as possible the cause of failure of the primary effort. Patients whose first operation was performed elsewhere are not included, since comparable technical and pathologic documentation is not possible.

There were 12 male and 67 female patients. The average age of 39.7 years at the time of the first operation closely approximates that of the entire series.

At the first operation 64 patients classified as group III by our classification;[10] 16 were in group IV. At the time of the second operation 21 of the original group III patients were classified as group IV, and 4 of the former group IV patients were in group III. Therefore there were 47 group III and 33 group IV patients at the time of reoperation.

Classification of Patients and Results

The opportunity to palpate the valve a second time and to compare the findings with a detailed diagram and operative note made at the time of the first operation permits a retrospective analysis of factors responsible for deterioration that can be gained in no other way. In an analysis of these data all but 2 of the patients were arbitrarily classified in 3 main groups: (1) unsatisfactory initial operation without significant insufficiency; (2) restenosis without insufficiency; (3) mitral insufficiency.

1. Unsatisfactory Initial Operation without Significant Insufficiency

This group was defined as one in which the valve area after manipulation was estimated to measure 2.5 cm.^{2} or less, or in 5 instances where the postoperative area of 3.0 cm.^{2} or more had been accomplished more by dilatation than by separation of the commissures.* Advanced scarring was the chief reason for such unsatisfactory operations. Whether this resulted in fracture-dilatation only, the opening of only one commissure, or from a failure to appreciate and manage secondary stenosis due to fusion of chordae, the result was the same, i.e., inadequate mobilization. Although the patient might be relieved rather dramatically of symptoms by the resulting increment in valve area, the stage was set for gradual loss of mobility and restriction of leaflets or actual refusion of the commissures by fibrin. There were 18 patients in whom it was judged that an unsatisfactory valvuloplasty had been effected initially but in whom mitral insufficiency of greater than minimal extent was not present (table 1).

Leaflet calcification sufficient to limit the initial operative opening was present in 5 of the patients with unsatisfactory procedures and developed or increased between operations in 2 others.

2. Restenosis without Insufficiency

This category was used in 28 patients in whom the valve had been opened to 3.0 cm.^{2} or more at the initial procedure but was found to be 1.0 cm.^{2} or less at reexploration. In 4 additional instances the valve area was estimated to be between 1.2 and 1.5 cm.^{2} at the time of the second operation. This group differs only in degree from those classified as "unsatisfactory initial operation" and the factors responsible for their failure to maintain improvement are the same. It is of interest that in this group of 32 patients only 1 commissure was fractured in 23, marked fusion of the chordae tendineae was present 18 times, and in 15 patients marked valvular calcification was present at the first operation or developed or increased between operations. In only 2 patients did restenosis occur in the absence of any of these factors. Thus in 30 of the 32 patients, conditions conducive to an unsatisfactory valvuloplasty were present.

A recurrence of acute rheumatic fever occurred between the first and second operations in 8 patients. It was thought to have been an important causative factor in the deterioration of 1 patient with an initially unsatisfactory operation and of 5 in the restenosis category.

3. Mitral Insufficiency

This group has been previously shown to be second only to inadequate initial surgery as a cause of deterioration after mitral valvuloplasty.[1] In this series of patients who were reexplored it was thought to be of significant degree (moderate or marked) in 28 of the 80. In all of these patients significant mitral stenosis was clinically diagnosed preoperatively, although in 26 a clinical diagnosis of significant associated insufficiency was also made. It was considered preoperatively, however, that operation for the relief of the stenosis present should give substantial clinical improvement. Now most of these patients would be operated upon by open technic under cardiopulmonary bypass to correct the associated mitral insufficiency.

Of these 28 there were 9 in whom the regurgitation was present at the time of the first operation, 11 in whom it was increased by the surgeon, and 8 in whom it appeared to have developed in the interval between operations. In half of these patients some restenosis had occurred between operations. In all of the patients with restenosis, factors leading to an unsatisfactory valvuloplasty were present.

Two of the patients are not included in the foregoing categories. In 1 it was thought in retrospect that she suffered predominantly from hypertensive heart disease at the time of both the first and second operations, although a small amount of restenosis had occurred. In the other a diagnosis of recurrent mitral stenosis was supported by catheterization findings. At operation, however, very minor stenosis was present (valve area greater

*This figure refers to the effective hemodynamic size.

Table 1

Factors Involved in the Findings at Two Operations (two or more factors usually present in any given patient)

Factors	Unsatisfactory	Restenosis	Mitral insufficiency Without significant restenosis	Mitral insufficiency With restenosis
1 Commissure only fractured	3	23	—	—
Fracture dilatation or poor fracture	15	0	2	2
Immobile or poor flexibility	2	6	1	3
Chordae fusion plus 2 or more	9	18	3	6
Calcification plus 2 or more at first operation	5	10	5	12
Calcification increased or developed	2	5	1	1
Mitral insufficiency plus 2 or more at first operation			5	4
Mitral insufficiency increased			5	6
Mitral insufficiency developed			4	4
Rheumatic fever	1	5	2	—
None		2		
Total patients	18	32	14	14
Grand total — 78				

There were 2 additional patients; one with hypertensive heart disease at both operations who had some degree of restenosis due to a poor fracture at the first operation, and another who had very little restenosis.

than 2 cm.^{2}) and no insufficiency. Her symptoms were presumably largely functional in nature, occurring at the time of the onset of atrial fibrillation several months before the second operation.

The median time for the duration of maximum improvement fell between 2 and 3 years. On the average, patients came to reoperation about 2 years after they had begun to deteriorate.

When the patients are analyzed according to their place in the series of the first 1,000 valvuloplasties for mitral stenosis, a decreasing incidence of reoperation is found. Fifty-four of the first 500 underwent a second operation as contrasted with 21 of those between 501 and 1,000. In order to eliminate the factor of natural attrition with time, the incidence of reoperation within 5 years of the first procedure has been analyzed. The first 800 patients were all operated upon at least 5 years prior to the date of this report. Therefore the number of patients reoperated upon in these 5 years in the 1 to 400 part of the series has been compared to those in the 401 to 800 category; namely, 26 versus 19. Chi-square analysis indicates no significant difference. If patients in whom a second operation has been done elsewhere within 5 years are included, the numbers would be 30 versus 22, still not significant. Nevertheless as experience has been gained in selection, technical proficiency, and the application of the newer principles of mobilization, as in the second 1,000, one would anticipate that fewer patients will require reoperation in future years.

Results Following Reoperation

Following reoperation, the patients as a group have not done as well as patients in the initial series of 1,000 operations. This is not surprising. Patients who have deteriorated often pose special technical problems for the surgeon, since many of the valves have defied the surgeon's best efforts originally. The group is thus specifically preselected with an emphasis on badly scarred valves. Reoperation is complicated not only by difficulty of access through pleural and pericardial adhesions that obscure the left atrial wall plus an amputated atrial appendage, but also by a more difficult pathologic valve process. Finally and most important is the fact that with all of the handicaps outlined above, 60 of the 80 operations were the original or standard direct atriotomy. In this, deliberate, well-controlled,

versatile intracardiac manipulation was impossible owing to poor hemostatic controls.

In this series of 80 reoperations, 60 were performed by the outmoded technic. In the group of 60 there were 6 operative deaths. The remaining 20 were operated by the new technic with 1 death. Of the 60 original-type reoperations with 6 deaths, 51 have been followed a year or more, 1 has been lost to follow-up, 1 was operated on less than 1 year ago, and 1 hypertensive patient, has been removed from the series. The operative mortality of this original group was 10 per cent, with no mortality in group III and 19 per cent in group IV. These mortality figures are comparable to the operative mortality figures for the first 1,000 patients undergoing primary valvuloplasty in our series.

Of the 51 having the original type of reoperation, only 22 or 43 per cent, were significantly improved 1 or more years later. However, when the patients are divided according to the reason for reoperation as outlined above, interesting differences appear. Of the patients with mitral insufficiency only 2 of 9, or 22 per cent, are improved, although 4 of 10 patients with mitral insufficiency plus restenosis were helped. Of those in whom the first operation was unsatisfactory, 4 of 14, or 28 per cent, are improved. Of those in whom restenosis was thought to have occurred, however, 14 of 18, or 78 per cent, are improved. This difference in the results of patients with restenosis compared to those with an unsatisfactory operation and mitral insufficiency is significant ($p<0.01$).

There was no relation between the length of follow-up after the second operation and the percentage of patients improved.

In short, these results demanded changes in selection and in technic. Those with mitral insufficiency are now operated upon with cardiopulmonary bypass. Those with stenosis are operated on by the better-controlled, more deliberate new tunnel technic. The tunnel technic allows emphasis of separation of posteromedial fusion zone and mobilization of subjacent chordae.

In the 20 operated upon by this technic in this series of 80 reoperations, there has been 1 operative death, a group IV patient with mitral insufficiency. The technic was instituted as a routine in October 1958. Only 2 of the patients have been followed over 1 year and both are markedly improved.

Although the follow-up observation of the remaining 17 patients is not long, the short-term course has been favorable. The surgeon's prognosis at operation in the first 1,000 valvuloplasties was remarkably accurate after long-term follow-up. Therefore the operator's estimates are likely to be valid in this group of tunnel reoperations with anterior and posterior medial mobilization.

General Consideration for Reoperation

In planning the approach for a reoperation for mitral stenosis one is attracted by the possibility of using the adhesion-free right pleural space and the right side of the left atrium as advocated by Bailey.[2] Experience with this technic points up its inadequacy for managing the anterior commissure because of its distance from the atriotomy and the inability to apply effective counterpressure on the ventricular wall, at and below the annulus.

The right-sided approach does have validity insofar as it reemphasizes crescentic posteromedial commissural opening rather than direct posterior valvotomy. It appears to be common practice throughout the world to open only the anterior commissure because this is simpler and results in significant clinical improvement. Indeed the vast majority of our first 1,000 patients had only anterior fusion bridge fracture. Where there is extensive thickening or calcification of the posteromedial half of the stenotic orifice it is apparent that anterior commissural opening alone may correct the stenosis very little. This rigid horseshoe that limits the orifice from opening disappears with posteromedial opening.

Where the fractures occur in the methods of Logan,[5] Tubbs,[6] and Dubost,[9] inserting a valvulotome through the ventricle or atrium and guided by a finger in the left atrium must depend in part on luck rather than control. Furthermore, this maneuver can only initiate

the fracture. Optimal mobilization still necessitates finger dissection of the chordae, one from another and away from the wall of the ventricle.

Open operation with cardiopulmonary bypass has a certain validity, particularly when significant mitral insufficiency must also be corrected or when the pathologic process is known to be impossible to correct by closed technic. The bypass procedure is certainly more cumbersome, however, and exposes the patient to a greater operative risk. At the same time leaflet mobility and the degree of insufficiency produced are less easily evaluated at open operation. Experience with open correction of mitral stenosis has, paradoxically enough, been very disappointing. It seems possible that advocacy of "routine open operation" may indicate a lack of familiarity with really good closed valvuloplasty or limited experience with open-heart surgery.

On 2 occasions superior pulmonary veins were used. This approach was a "strategic retreat" in the face of an inadequate appendage, a hold-over from our very early experience.[10] This proved unsatisfactory because of the position of the valve and the danger of serious damage to the venous drainage of the left upper lobe. In one patient these limitations defeated the second attempt, and a third operation was necessary, which was successful.

The New Technic of Reoperation

With the patient in the lateral decubitus position with the left side up, the fourth or fifth interspace is opened. If there is heavy calcification in the valve, the head vessels are isolated. The pericardium is reopened and the surface of the left atrium exposed. It was our former practice to place 2 or 3 concentric purse-string sutures on this flat surface of the atrial wall. Following this a stab wound was made in the center of the circumscribed area. The fifth finger was inserted carefully to open the atriotomy enough to accept the index finger. The valvuloplasty was then carried out with the finger alone or aided by one of the breadknife valvulotomes described previously.[11] Hemostatic control was precarious. There were harrowing experiences with hemorrhage and tears of the atrium. Fortunately there were no deaths, but the valve manipulation was hurried. Thus a new technic has been developed and used in the last 20 operations of this report.

The new operation is entirely similar up to entry into the left atrium. At this point instead of placing concentric purse-string sutures, an Ivalon tunnel similar to that used in transaortic valvuloplasty[12, 13] is sewed to the exposed atrial wall. While an assistant controls the tunnel with a Rumel tourniquet, the surgeon makes an incision in the atrial wall with the tunnel and inserts his finger. Once in the atrium he has excellent control and any necessary manipulations can be undertaken without fear of an uncontrollable hemorrhage or tear into the atrium.

A cardinal advantage in this new technic is the opportunity it affords the operator to have an assistant occlude the atriotomy with his finger while the surgeon goes to the opposite side of the table (facing the patient's anterior chest wall) in order to open the posterior commissure. This commissure is recognized by all experienced in the field as the more difficult to fracture. From a position in front of the patient it is possible, however, to open virtually all the adherent components. The bare finger generally initiates the fracture posteromedially by following up the chordae to the major leaflet and fracturing it with a counterclockwise motion. If this fails, the concave posteromedial fusion zone can often be incised, stretched, then fractured with a fingernail and finger preparing for the counterclockwise motion to open the commissure. In such situations there is commonly fusion of the chordae to each other and to the posterior wall of the ventricle that limits adequate leaflet mobility. This must be corrected by meticulous finger dissection. At times considerable force is necessary and attention must be given to the point of insertion of the left pulmonary veins into the left atrium, lest a tear occur. If the surgeon's left hand is passed to the posteromedial aspect of the heart, counterpressure can be exerted. Rarely will

the valvulotome on the finger or inserted through the left ventricle be necessary.

This meticulous, complete leaflet mobilization, directed first toward the anterior commissure and its subvalvular components as the surgeon stands behind the patient and then to the posteromedial fusion zone and subvalvular components with the surgeon in front of the patient, is just as important at initial operations as at reoperations. It is described here simply because it has not been emphasized in previous publications and was not routinely possible during reoperation until the operating tunnel was used.

The more adequate mobilization of these difficult valves afforded by this technic will certainly improve the results in reoperations. Indeed, application of these concepts to primary operation may reduce the incidence of reoperation. Open procedures for these problems have been disappointing; at the same time closed technic has improved. Unless insufficiency is the dominant lesion or valve replacement is contemplated, there has been a recent trend away from open operation.

Summary

A series of 80 reoperations for mitral stenosis in 79 patients is reported and analyzed.

The most important causes of deterioration after valvuloplasty for mitral stenosis are inadequate initial operation, restenosis, and mitral insufficiency. Generally more than one of these factors pertain.

An adequate mitral valvuloplasty requires the complete opening of both the anterior and posteromedial commissures and the mobilization of the chordae tendineae from each other and from the wall of the ventricle.

The advantages and limitations of closed reoperation, open reoperation, the right-sided approach, and the use of the transventricular valvulotome are reviewed.

More complete correction of stenosis with mobilization of posteromedial, anterior, and subvalvular chordae is emphasized. This is attained by operating from both the ventral and dorsal aspects of the patient through a left posterolateral thoracotomy incision.

An Ivalon operating tunnel sutured to the left atrial wall at reoperation makes it possible to carry out the more extensive valvuloplasty at reoperations.

A lower operative mortality, better long-term results, and fewer instances of deterioration are anticipated when this concept of improved valvuloplasty is effected initially.

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Raynaud's Disease with Sclerodactylia

A Follow-Up Study of Seventy-one Patients

By RICHARD G. FARMER, M.D., RAY W. GIFFORD, JR., M.D., AND EDGAR A. HINES, JR., M.D.

DURING the course of previous studies of Raynaud's disease in women and girls,[1] and of patients with systemic scleroderma,[2] we encountered the records of 71 patients with Raynaud's disease and secondary sclerodermatous changes confined to the digits (sclerodactylia). These patients all had Raynaud's disease as defined by the criteria of Allen and Brown,[3] namely: (1) episodes of Raynaud's phenomenon precipitated by cold or emotion, (2) bilaterality of the phenomenon, (3) absence of gangrene or the presence of only minimal degrees of cutaneous gangrene of the digits, (4) absence of any systemic disease that might account for the occurrence of Raynaud's phenomenon, and (5) duration of symptoms of 2 years or longer. In addition to the Raynaud's disease, all 71 patients had sclerodermatous changes in one or more digits when first examined at the Mayo Clinic, but none had any evidence of cutaneous sclerosis in other sites or of systemic scleroderma.

Because of the confusion that has resulted from the various classifications of scleroderma, and in light of O'Leary and Waisman's contention[4] that patients with Raynaud's disease and sclerodactylia should be considered to have systemic scleroderma of a type that they called "acrosclerosis," it was thought worth while to conduct a follow-up study of these patients. Follow-up information was obtained from all of the patients at re-examination at the clinic or by correspondence or both.

Preliminary Observations

The 71 verified cases of Raynaud's disease were divided into a medical group (40 patients) and a surgical group (31 patients), depending on whether or not a cervicothoracic sympathectomy had been performed for the relief of symptoms. The ages of the medically treated patients ranged from 22 to 68 years (average 39.3) at the time of the original diagnosis at the clinic. The ages of the patients treated surgically ranged from 18 to 56 years (average 35.5). The average age for the entire group was 37.6 years (table 1). Only 5 patients (7 per cent) were men; however, many of the cases were selected from a group that had included only women.[1]

At the time of the original diagnosis, trophic changes of the digits (ulcerations, fissuring, chronic paronychiae) had been observed in 26 of the 71 patients (36.6 per cent); 15 of the 26 were subsequently treated by means of cervicothoracic sympathectomy. Amputations of digits had been performed for 3 patients (4 per cent), involving amputation of single digits in 2 instances and of 2 digits in 1 case. These were performed primarily because of the presence of trophic changes; extensive gangrene was not observed.

Results of Follow-up Study

Except for 1 patient who died within a year, the time of follow-up after the original diagnosis at the clinic ranged from 2 to 31 years, the average being about 10 years for the entire group. Of the 40 patients treated medically, 10 reported that the condition had improved, 10 thought it worse, and 17 believed it was unchanged. Three patients were dead. Among the 31 patients treated surgically, 10 believed the condition to be better, 6 worse, and 12 about the same (table 2). Three were dead.

Trophic changes of the digits had developed subsequent to the time of initial examination in 3 of the patients treated medically and 5 of the patients treated surgically.

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Table 1

Ages at Time of Original Diagnosis of Seventy-one Patients with Raynaud's Disease and Sclerodactylia; Category of Treatment

Age, years	Medical treatment	Surgical treatment
9-20	2	1
21-30	9	11
31-40	12	6
41-50	10	10
51-60	6	3
61 or more	1	0
Total	40	31
Average age	39.3 yr.	35.5 yr.
For whole group	37.6 yr.	

Table 2

Follow-up Information Regarding Sixty-five Living Patients with Raynaud's Disease and Sclerodactylia

Condition of Raynaud's phenomenon and sclerodactylia	Medical group		Surgical group	
	No.	Per cent	No.	Per cent
Better	10	27	10	36
Same	17	46	12	43
Worse	10	27	6	21
Total	37	100	28	100

Of the 6 patients who died (8.4 per cent), 2 died of cerebrovascular accidents, and 1 each of coronary arterial disease, cirrhosis of the liver, pneumonia, and ovarian carcinoma. None of the patients who died had systemic scleroderma. The average age at the time of death was 49.7 years, and death occurred on an average of 4.7 years after the diagnosis of Raynaud's disease had been made at the clinic (table 3).

Systemic scleroderma apparently had developed in 3 of the 71 patients (4 per cent). Brief reports of their cases follow.

Report of Cases

Case 1

A 48-year-old woman, first seen at the clinic in 1940, had had Raynaud's phenomenon, involving both hands, for 15 years; trophic changes had been present for 5 years. Scleroderma of the fingers was observed. All peripheral arteries were pulsating normally, and no primary systemic disease or organic arterial disorder could be found. A letter from the patient in 1948 indicated that the Raynaud's phenomenon had involved the feet also and that the scleroderma had extended to the arms, chest, and face. A report in 1951 stated that the scleroderma had progressed and that the patient had a "heart ailment." According to a letter received in January 1960, the sclerosis has remained about the same, but the patient now has dysphagia.

Table 3

Raynaud's Disease with Sclerodactylia: Information Regarding Six Patients Who Died during Follow-up Period

Age at death, years	Time of death after diagnosis, years	Cause of death
51	2	Coronary arterial disease
62	5	Cerebrovascular disease
42	1	Cirrhosis of liver
49	7	Cerebrovascular disease
33	7	Pneumonia
62	6	Ovarian carcinoma
49.7	4.7	Average

Case 2

A 21-year-old woman was seen at the clinic in 1942 with Raynaud's phenomenon, involving both hands, which had been present for 5 years. No underlying cause could be determined, and no trophic changes were found, but sclerodactylia was noted. All peripheral arteries were pulsating normally. A cervicothoracic sympathectomy was performed. A follow-up letter in 1951 revealed that the sclerosis had increased and involved both arms as well as the hands; trophic changes of the digits had developed. In addition, progressive dysphagia had been present for 6 years.

Case 3

A 23-year-old woman was first seen at the clinic in 1926 with Raynaud's phenomenon, involving the hands, of 6 years' duration. Trophic changes and sclerodactylia were present. The peripheral arteries were pulsating normally, and no primary systemic disease or organic arterial disorder was found. A right cervical sympathetic ramisection was performed at that time. The patient returned in 1932, and because of a poor result from the first operation a bilateral cervicothoracic sympathetic ganglionectomy was performed. A letter from her physician in 1943 described changes involving the arms, face, and hands that were consistent with a diagnosis of scleroderma. The patient was seen again at the clinic in 1957, and a diagnosis of scleroderma was made. At this time the Raynaud's phenomenon was unchanged, but sclerodermatous changes of

the skin on the hands, arms, face, and trunk were noted. Calcinosis cutis was present in the hands, and there were trophic changes of the digits. A letter received in January 1960 indicated that the patient's condition has remained about the same.

In the first 2 cases the subsequent diagnosis of systemic scleroderma is only presumptive; however, the subjective complaints by the patients make this diagnosis likely. The third patient was re-examined at the clinic and the diagnosis of systemic scleroderma was confirmed.

Discussion

The relationship between systemic scleroderma and sclerodermatous changes confined to the digits (sclerodactylia) occurring secondary to long-standing Raynaud's disease has not been clear. However, in this study only 4 per cent of the patients who originally had Raynaud's disease and sclerodactylia were found to have developed systemic scleroderma, and there seems to be no justification for the belief that the two are the same disease. The incidence of sclerodactylia has been reported as being 10 to 12 per cent among patients with Raynaud's disease.[1, 4] It should be emphasized that sclerodactylia is often a late development and, as the current study bears out, is frequently associated with trophic changes. The total number of patients with trophic changes, including those in whom these changes developed during the period of follow-up, was 34 (48 per cent).

As mentioned, only patients who had Raynaud's phenomenon for at least 2 years prior to the diagnosis of Raynaud's disease were included in this study. Sclerodermatous changes in the digits among patients who have had Raynaud's phenomenon for less than 2 years often represent an early sign of systemic scleroderma. However, after the diagnosis of Raynaud's disease has been established, the development of sclerodactylia will be followed by systemic involvement only rarely (4 per cent in this study). The use of strict criteria for the diagnosis of Raynaud's disease will help to prevent mistakes in distinguishing between systemic scleroderma with secondary Raynaud's phenomenon and Raynaud's disease with sclerodactylia. The correct diagnosis is important because of the vastly different prognosis of these two conditions.

A recent study[2] of 271 patients with systemic scleroderma revealed that about half of those who were traced died during a follow-up period which averaged 8.5 years. However, in the current series of 71 patients with Raynaud's disease and sclerodactylia, only 8.4 per cent died during the follow-up period, and none of these had systemic scleroderma.

Summary and Conclusions

The records of 71 patients with Raynaud's disease and sclerodactylia seen at the Mayo Clinic were studied. Follow-up information was obtained for all, with periods varying from 1 to 31 years. Systemic scleroderma seemed to have developed in only 3 patients. Six patients had died but none from systemic scleroderma. This study does not support the belief that systemic scleroderma and sclerodactylia secondary to Raynaud's disease are the same disease.

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Pulmonary Artery Banding

A Treatment for Infants with Intractable Cardiac Failure due to Interventricular Septal Defects

By HAROLD M. ALBERT, M.D., RICHARD L. FOWLER, M.D., CLAUDE C. CRAIGHEAD, M.D., BERTRAM A. GLASS, M.D., AND MOHAMMAD ATIK, M.D.

INFANTS born with interventricular septal defects may encounter little difficulty during the first year of life. Although a number develop varying degrees of cardiac failure, most of these respond to digitalization so that by the end of the first year retarded growth and cardiac failure are no longer significant problems. A few, however, within the first weeks of life, develop cardiac failure that is refractory even to vigorous medical therapy. They are likely to die early and suddenly. Surgical management of this type of case is the subject of this report.

Ideal treatment for these infants should be closure of the interventricular septal defect. Unfortunately, they are poor candidates for open-heart surgery. Reported results indicate an unfavorable prognosis in those under 2 years of age so treated. Even in experienced hands mortality is 40 per cent or higher. There are no reports of such a series in infants under 1 year of age, but the mortality would probably be higher. What is needed, then, is a relatively simple operation to tide the child over this critical period so that curative surgery can be accomplished at a later date.

Muller and Dammann,[1] basing their technic on the experimental work of Holman and Beck,[2] and Hufnagel, Roe, and Barger[3] reported the production of pulmonary stenosis by wedge and suture of the pulmonary artery. Inasmuch as the patients were desperately ill and the operations extensive, mortality was 50 per cent. Their technic has been modified by us so that it consists of merely banding the base of the pulmonary artery with tape.

In the case of a large interventricular septal defect, the separate ventricles with a free communication act in many ways as a single chamber. Ordinarily vascular resistance is low in the pulmonary and high in the systemic circulation. Thus, most of the blood makes its way into the circulation of low resistance, i.e., the pulmonary circulation.

By placing a band around the main pulmonary artery, flow in the lesser circulation is impeded. Hence, excessive flow through the lungs, which leads to cardiac decompensation, is diminished. In addition, buildup of pressure within the pulmonary circuit, which may lead to increased pulmonary resistance with ensuing vascular changes, is prevented.

Twenty infants with interventricular septal defects producing intractable cardiac failure have had banding of the pulmonary artery. Their ages ranged from 3 weeks to 18 months. All but two were under 6 months of age. All were extremely ill, dyspneic, underdeveloped babies. Repeated respiratory infections were common, and treatment of bronchiolitis and pneumonitis was difficult because of concomitant cardiac failure.

The diagnosis of interventricular septal defect was suspected in each because of the presence of a rough systolic murmur, cardiomegaly, hepatomegaly, and splenomegaly associated with radiologic evidence of plethoric lung fields. The electrocardiogram showed either right or combined ventricular hypertrophy. Cardiac failure and respiratory infection were treated intensively. As soon as infection was controlled, cardiac catheterization was performed to confirm the diagnosis. In each instance, large left-to-right shunts

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Supported in part by research grant H-2573 from the National Heart Institute, U. S. Public Health Service.

were found at the ventricular level and pulmonary hypertension was invariably present. Although an initial improvement usually followed the administration of digitalis and diuretics, cardiac failure could not be completely controlled. Even with the most vigorous medical treatment, these patients remained in moderate to severe cardiac failure. Only under such circumstances were patients considered for surgery.

Technic

With the infant supine or rotated slightly to the right, the left hemithorax was entered through an anterolateral incision in the third or fourth interspace. Patent ductus arteriosus was excluded by appropriate exploration.

The pericardium was opened widely to expose the right ventricle and pulmonary artery. The left atrial appendage was moved aside and the grooved indentation between the base of the pulmonary artery and aorta was found with the tip of a Moynihan clamp. At this point only two layers of visceral pericardium separate the vessels so that the clamp was easily passed around the pulmonary artery at its base. Umbilical tape was placed to encircle the pulmonary artery and the ends were passed through a Rummel tourniquet (fig. 1A).

Nineteen-gage needles attached to transducers were introduced into both the pulmonary artery and right ventricle for continuous monitoring of pressures. With the aid of the Rummel tourniquet, the tape was tightened (fig. 1A) gradually until pressure in the pulmonary artery dropped to slightly above normal limits and the pressure curve showed some flattening.[4] Simultaneously the right ventricular pressure increased to approximately that of the left ventricle (fig. 2). The heart was watched closely during this process, since excess tightening is reflected by slight dilatation of the right ventricle, abrupt slowing, and weakening of the heart. If this occurred, the tourniquet was released, the heart was allowed to recover, and the procedure was repeated. An acceptable degree of stenosis was usually reflected by a slight decrease in size of the right ventricle with

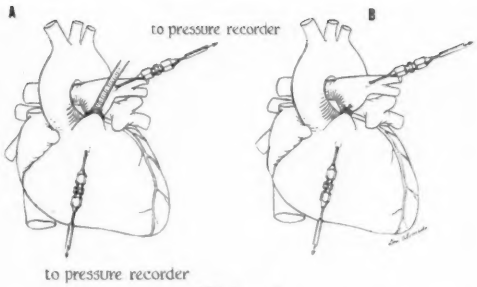

Figure 1

Technic of pulmonary artery banding and monitoring pressures in right ventricle and pulmonary artery.

little change in cardiac rate. If marked elevation of pulmonary vascular resistance has already occurred, the changes in pressure which can be accomplished are much less conspicuous and should not be pursued overzealously. A small gradient with flattening of the pulse wave may be accepted under such circumstances.

Once the desired gradient was achieved, the tape was fixed in position by ligating it with silk between the tip of the metal tourniquet and the pulmonary artery. On removal of the tourniquet, the tape was permanently fixed with silk sutures (fig. 1B). Occasionally on removal of the tourniquet the tape slipped. This was recognized immediately by a rise in the pulmonary artery pressure. When slipping occurred, additional narrowing was accomplished by placing another suture in the tape to tighten it. The band having been fixed at the correct degree of stenosis, the excess tape was cut off, leaving the ends a quarter of an inch long to facilitate removal at a later date. It should be noted that the band was placed at the base of the pulmonary artery so that no chamber intervened between the pulmonary valve and the band. The vessel was constricted from 60 to 80 per cent of its original diameter in order to effect adequate diminution in pressure distal to the constriction.

Typical Case History

This white baby boy (M.H., L.S.U. 58-307144) was born by spontaneous delivery following an uncomplicated pregnancy. No abnormality was noted until 7 weeks of age, when he was treated

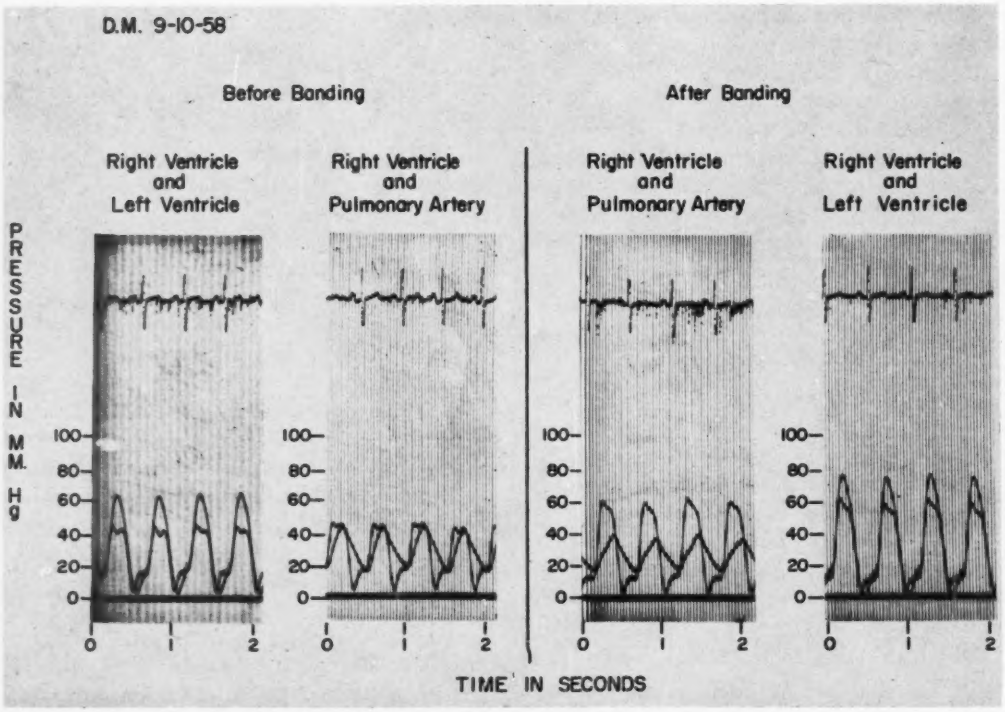

Figure 2

Typical pressure tracings before and after pulmonary artery banding. Note rise in left ventricular pressure after banding.

by his family physician for an upper respiratory infection and a murmur was noted.

At the age of 3 months he developed another respiratory infection. The murmur was noted to be louder, the pulse rate was very rapid, and the liver was enlarged. The child was digitalized, but did not improve, so he was sent to the hospital.

Physical examination revealed a poorly nourished boy in obvious respiratory distress. The pulse and heart rate were 140 per minute, and the respirations were 100 per minute and grunting with intercostal retraction. Loud sibilant, bubbling and crepitant rales as well as coarse rhonchi were heard throughout both lung fields. There was a thrill as well as a grade II to III harsh, systolic murmur along the left sternal border, loudest at the fourth intercostal space. The apex beat was palpable in the anterior axillary line.

The liver was palpable at the level of the umbilicus. The spleen and kidneys were palpable. The femoral pulses were normal. Physical examination was otherwise normal. The clinical impression was interventricular septal defect with pulmonary hypertension and congestive failure.

He improved with digitalis and antibiotic therapy and was discharged.

He was readmitted at the age of 6 months with a story of repeated bouts of upper respiratory infections and frequent cyanosis with crying.

Physical examination revealed an underweight infant with cardiomegaly, hepatomegaly, and splenomegaly, pulse rate of 120 and respiratory rate of 35 per minute. A grade II to III harsh systolic murmur was heard best in the fourth and fifth left intercostal spaces and it was transmitted to the left and back toward the angle of the scapula. Other than mild otitis media, the remainder of the physical examination was normal.

While awaiting cardiac catheterization, the child developed severe bronchiolitis and congestive failure that responded to treatment.

Data from cardiac catheterization were compatible with interventricular septal defect with a large left-to-right shunt. The pulmonary blood flow was calculated to be 3½ times the systemic flow. There was also pulmonary hypertension.

He again developed pneumonitis and congestive failure 1 week later and gradually responded to

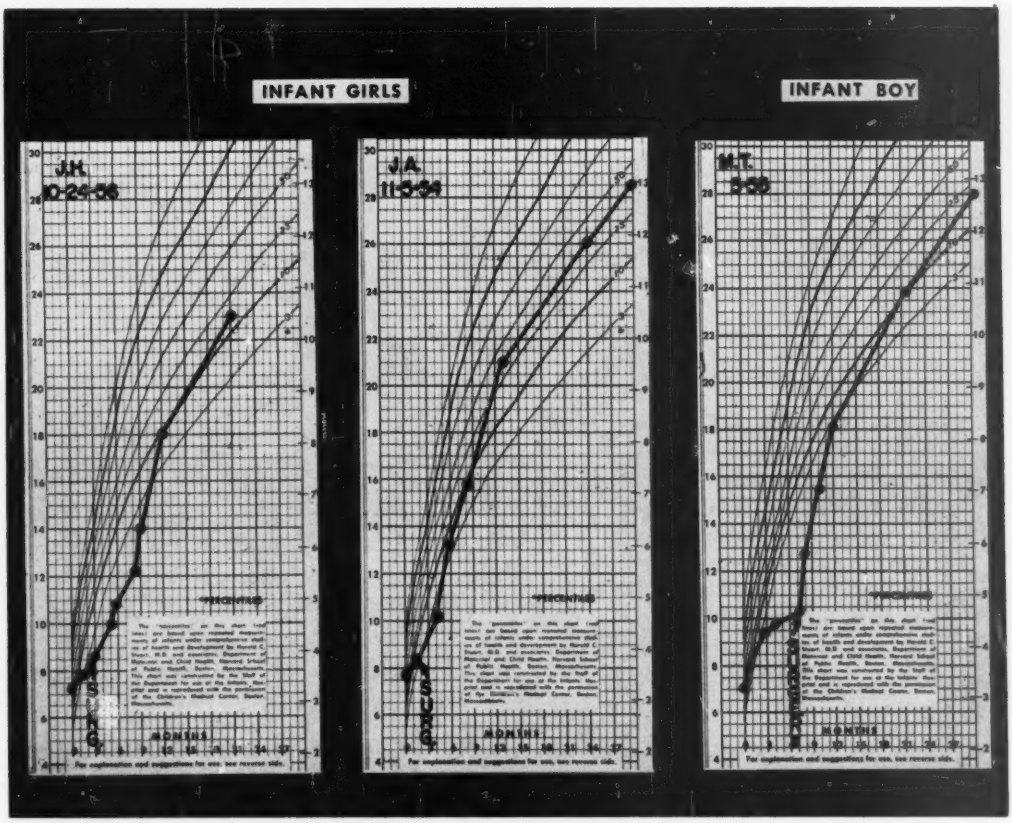

Figure 3

Typical growth curves. Note rapid upswing in curve after banding of pulmonary artery.

vigorous therapy. However, a few moist rales persisted at both bases and the liver remained palpable.

On March 3, 1959, surgery was performed following the technic described. Pressures measured prior to banding were 95/0-15 in the right ventricle and 60/15 in the main pulmonary artery. Aortic pressure was 100/50. At the conclusion of the procedure pressures were 110 to 115/0-6 in the right ventricle and 40/20 in the pulmonary artery.

Postoperatively the child was overtransfused through error and developed severe pulmonary edema, necessitating phlebotomy. Otherwise his postoperative course was uneventful. Five weeks after operation he had gained over 3 pounds in weight and had had no evidence of respiratory difficulties since discharge. He continued to do well and gain weight. He had experienced one or two mild episodes of upper respiratory infection but no serious illness and no cyanosis. Digitalis was discontinued. He was last seen 1 year after surgery and was doing well, with no evidence of failure and no further attacks of respiratory disease.

Results

Of 20 infants subjected to banding of the pulmonary artery, one died a few hours after operation due to unrecognized bleeding from the chest wall. Another died at home 2 months after operation following an acute illness. There was no autopsy, and the cause of death was not determined. Through error in pressure reading insufficient stenosis was produced in one infant so that rebanding was necessary 3 weeks after the first attempt. His subsequent convalescence was uneventful.

The postoperative course of the survivors has been remarkably smooth and the early change has been striking. The precordial heave

has usually diminished or disappeared at once. Within a few days the liver, which preoperatively had usually been quite large, has decreased in size until hardly palpable.

In a few, cardiac failure, which had been intractable prior to operation has completely disappeared within 2 weeks. In the remainder, failure has been easily controlled with digitalis and, after a period of readjustment of weeks to a few months, the drug has been stopped.

After a stabilizing period of about 3 months, the babies have made rapid strides until attaining a normal growth curve (fig. 3). There were two sets of twins and in each set, one twin was normal while the other required banding. After operation, both have caught up with their counterparts in height, weight, and activity.

Indications are that these children do well for approximately 3 to 5 years, then evidence a right-to-left shunt, and show the typical picture of a mild tetralogy of Fallot. When this occurs, the septal defect should be closed and the size of the pulmonary artery restored.

Discussion

To do a temporizing procedure when it is technically feasible to do a curative one may seem old fashioned. We believe, nonetheless, that the very low mortality associated with banding of the pulmonary artery, even though the infants are tiny and have intractable cardiac failure, makes the procedure attractive. The children come out of failure, grow, and approach the status of a standard risk for closure of the interventricular septal defect. Anticipated adhesions will admittedly make the definitive operation more difficult and possibly increase morbidity and mortality. Experimental work,[5] however, has indicated that removal of the band and restoration in size of the pulmonary artery are not formidable, so that the mortality from the two operations should be less than that from initial septal closure in these critically ill babies. An insufficient number of bands have been removed and defects closed to draw conclusions about comparative mortality.

Summary

The technic of banding the pulmonary artery is described.

Twenty infants with intractable cardiac failure secondary to interventricular septal defects have had banding with one operative and one late death.

The operation is palliative, and definitive surgery probably must be done when the child is 3 to 5 years of age.

Banding the pulmonary artery is a relatively safe procedure but the mortality of banding plus ventricular closure and unbanding remains to be evaluated.

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Precordial Scanning

Applications in the Detection of Left-to-Right Circulatory Shunts

By WILLIAM P. CORNELL, M.D., EUGENE BRAUNWALD, M.D., AND ANDREW G. MORROW, M.D.

ALTHOUGH the presence of a left-to-right cardiac shunt can be suspected from clinical findings, the development of catheterization of the right side of the heart[1] and the perfection of ancillary technics, such as inhaled[2, 3] or injected[4] inert foreign gases and indicator-dilution curves[5, 6] have greatly improved the detection, localization, and measurement of such shunts. In view of the slight but definite hazard[7] and the discomfort and expense attendant upon cardiac catheterization this method is applied primarily to patients in whom there is considerable clinical suspicion of the presence of a left-to-right shunt. The applications of precordial scanning, a simple, yet reliable technic for determining the presence or absence of such a shunt without catheterization of the heart are described in the present report.

In 1927 Blumgart and Weiss[8] first demonstrated the use of a precordial scanning technic in the measurement of the circulation time between a peripheral vein and the right side of the heart. Prinzmetal and his collaborators in 1949[9] reported observations on a single patient with a left-to-right cardiac shunt; following a peripheral venous injection of radioactive sodium (Na^{24}) continued recirculation through the heart and pulmonary circulation greatly slowed the clearance of the isotope from the central circulation and thereby prolonged the descending limb of the precordial dilution curve. More recently, a number of investigators[10–12] have confirmed the observation that precordial radioactivity curves are modified in a characteristic fashion by the presence of left-to-right circulatory shunts, congestive heart failure, and valvular regurgitation. The purpose of this communication is to present the results of precordial scanning in 75 patients. Preliminary observations have been reported previously.[13]

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Methods

Precordial scanning was carried out in 36 patients who were subsequently shown to have left-to-right circulatory shunts. These patients ranged in age from 2 to 52 years and their average age was 20 years. The presence of a left-to-right shunt was proved at operation in 28 patients, and by application of the inhaled Kr^{85} test[2] at right heart catheterization in all but one of the remainder; the exception, a 25-year-old woman with an atrial septal defect, had a small left-to-right shunt demonstrated by means of a dye-dilution curve with left atrial injection, although the Kr^{85} test was equivocal. In 17 patients the shunt entered the right atrium, in 16 it entered the right ventricle, and in 3 the pulmonary artery.

Thirty-nine patients studied were proved not to have cardiac shunts. In this group of patients 15, who ranged in age from 6 to 50 years, had systolic heart murmurs and were suspected of having left-to-right shunts. The results of right heart catheterization, however, showed unequivocally that none was present. The remaining 24 patients all had rheumatic heart disease and all of these were also studied by left heart catheterization. Most of these patients had cardiac enlargement and diminished cardiac reserve. Five were in frank congestive heart failure. Nine of these patients had clinical and hemodynamic evidence of either mitral or aortic valvular regurgitation. Two patients had clinical and hemodynamic evidence of tricuspid regurgitation in addition to involvement of the mitral valve.

The precordial scanning technic employed was a modification of that utilized by McIntyre and associates[14] and by Turner and collaborators.[10] A ¾-inch activated thallium-sodium iodide scintillation detector* was surrounded by a 1-inch collar of lead that extended 6.8 cm. beyond the face of the crystal. The aperture of this collimator was 3.8 cm. in diameter and was not tapered. The

*Model DS-1, Nuclear-Chicago Corporation.

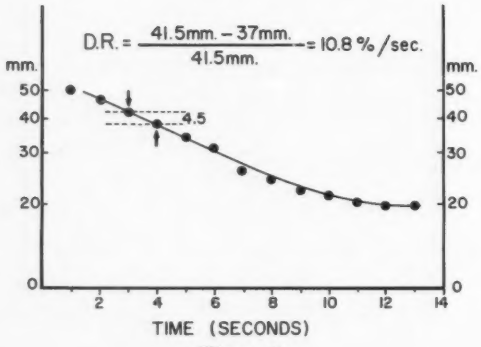

Figure 1

Method employed for calculating the disappearance rate (D.R.). The descending limb of the curve is plotted on semi-logarithmic paper and the rate of decline per second for the straight portion is determined. In the example the concentration fell from 41.5 mm. to 37 mm. in 1 second, representing a 10.8 per cent decline.

photomultiplier was used in conjunction with a count-rate meter† in which two thirds of full-scale response was attained in 1.5 seconds. The output of this rate meter was led into a rectilinear recorder,‡ which provided a time concentration-curve of the total radioactivity beneath the scintillation detector. The scintillation detector was placed so that the center of the opening in the collimator was in the midsternal line at the fourth intercostal space. The bottom surface of the collimator just touched the patient's skin; 10 to 150 μc. of I^{131}-labeled Diodrast§ were then rapidly injected into the right antecubital vein and flushed with 10 ml. of saline.

The curves were analyzed (1) by replotting the descending limb of the curve on semi-logarithmic paper and calculating the rate of disappearance of the isotope during the early portion of the descending limb and expressing this as the percentage of decline of isotope concentration per second[15] (fig. 1); (2) by determining the build-up time, i. e., the time interval between the appearance of radioactivity in the right side of the heart and the peak of that portion of the curve resulting from the isotope in the left ventricle; and (3) by calculating the product of disappearance rate and build-up time.

Results

The results are presented in tables 1 and 2

†Model 1615-B, Nuclear-Chicago Corporation.

‡Recti-riter, Texas Instruments, Houston, Texas.

§Obtained from Abbott Laboratories, North Chicago, Illinois.

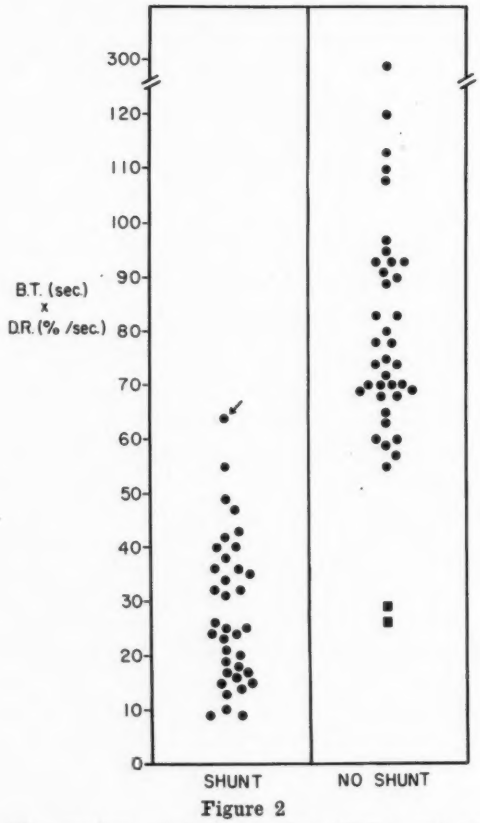

Figure 2

The product of build-up time (B.T.) and of disappearance rate (D.R.) in patients with and without left-to-right shunts. The arrow points to the value derived from the patient with the very small atrial septal defect discussed in the text. The 2 patients with tricuspid regurgitation are indicated by the squares.

and are summarized in figs. 2 and 3. Representative curves are reproduced in figs. 4, 5, and 6.

The patients with left-to-right shunts had build-up times that ranged from 3.5 to 19.0 seconds and the mean was 8.0 seconds. Because of the recirculation of indicator the disappearance rate was relatively low (1.3 to 11 per cent per second, mean = 3.8 per cent per second). The product of these two parameters ranged from 9.1 to 64.8 with a mean of 28.1. The two highest values of the product of the build-up time and disappearance rate

Table 1

Results of Precordial Scanning in Patients with Left-to-Right Shunts

Patient	Age (yr.)	P.F./S.F.	B. T. (sec.)	D. R. (% sec.)	B. T. X D.R.
Atrial septal defect					
J. K.	25	1.1/1.0	9.0	7.2	64.8
G. B.	13	1.5/1.0	5.0	1.9	9.5
D. R.	17	1.6/1.0	8.0	4.8	38.4
J. R.	11	1.7/1.0	6.0	6.0	36.0
L. Z.	7	1.7/1.0	5.0	5.1	25.5
V. C.	39	1.8/1.0	12.0	3.5	42.0
E. F.	29	1.9/1.0	5.0	3.3	16.5
R. T.	42	1.9/1.0	7.0	3.0	21.0
N. R.	31	2.0/1.0	10.0	3.5	35.0
E. T.	52	2.2/1.0	7.0	2.8	19.6
D. K.	33	2.3/1.0	8.0	2.3	18.4
D. B.	40	2.4/1.0	9.0	4.1	36.9
A. M.	31	2.4/1.0	6.0	2.3	13.8
E. R.	19	2.6/1.0	10.0	3.4	34.0
L. D.	46	3.3/1.0	10.0	2.5	25.0
W. L.	23	4.1/1.0	7.0	2.2	15.4
L. F.	18		16.0	2.0	32.0
Ventricular septal defect					
R. M.	7	1.15/1.0	4.0	7.9	31.6
A. M.	14	1.3 /1.0	7.0	6.8	47.6
C. C.	25	1.35/1.0	11.0	3.7	40.7
G. C.	6	1.35/1.0	7.0	2.9	20.3
W. M.	18	1.35/1.0	13.0	3.3	42.9
A. N.	8	1.4 /1.0	6.0	4.4	26.4
G. M.	24	2.0 /1.0	3.5	5.0	17.5
D. K.	12	2.2 /1.0	9.0	2.6	23.4
B. S.	8	2.2 /1.0	9.0	4.5	40.5
R. N.	8	2.6 /1.0	9.0	1.9	17.1
N. H.	6	3.3 /1.0	7.0	1.3	9.1
D. B.	8	3.5 /1.0	4.0	2.5	10.0
E. B.	15	3.9 /1.0	7.5	2.2	16.5
M. S.	13	6.5 /1.0	7.0	2.2	15.4
D. M.	9		10.0	2.4	24.0
Patent ductus arteriosus					
W. A.	16	1.2 /1.0	7.0	7.0	49.0
A. K.	2	1.55/1.0	5.0	11.0	55.0
S. W.	50	4.9 /1.0	19.0	1.3	24.7
Transposition of great vessels					
D. K.	10		4.0	3.7	14.8

Abbreviations: P.F./S.F. = Pulmonary to systemic flow ratio. B. T. = Build-up time. D. R. = Disappearance rate.

exceeded the lowest values observed in the group without shunts. One of these high values was obtained from the patient with the very small left-to-right shunt at the atrial level described above. The other was from a 2-year-old boy with a small patent ductus arteriosus and a pulmonary/systemic flow ratio of 1.5/1.0.

In the patients without left-to-right shunts who had functional heart murmurs or rheumatic heart disease without heart failure the build-up times ranged from 5.0 to 14.0, with

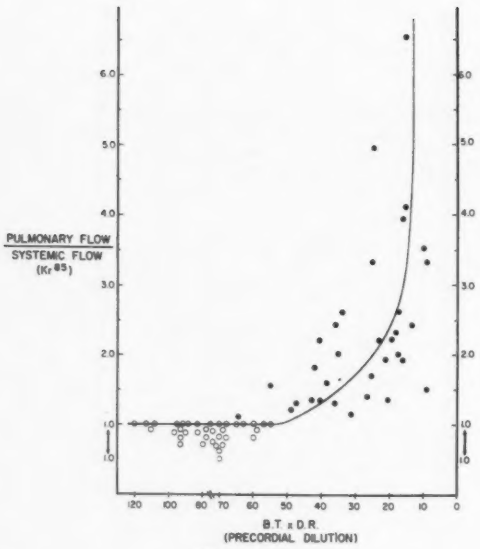

Figure 3

Relationship between the pulmonary/systemic flow ratio determined by the Kr^{85} technic and the build-up time disappearance rate product determined by the precordial scanning technic. Open circles represent data obtained from patients without left-to-right shunts and closed circles data obtained from patients with left-to-right shunts.

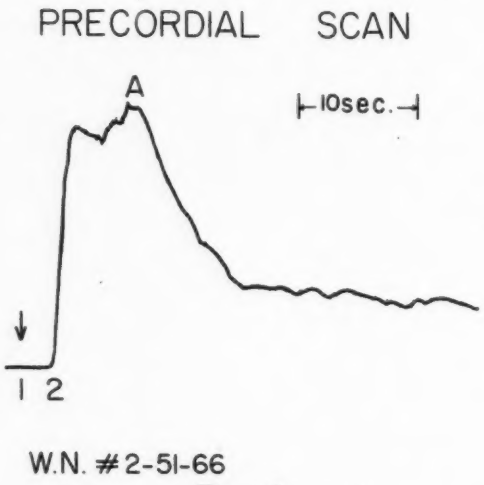

Figure 4

Representative curve obtained from a patient without heart disease. Vertical arrow at 1 represents the instant of injection; 2 represents the appearance of the isotope in the right heart and A the peak of the concentration in the left ventricle. The time interval between 2 and A represents the build-up time.

an average of 8.8 seconds. The disappearance rates were higher than in the patients with shunts, and the products of build-up time and disappearance rate were, therefore, also higher and ranged from 55.0 to 120.0, with a mean of 79.3. On the other hand, in the patients without left-to-right shunts with rheumatic heart disease and heart failure the build-up times were longer, 20.0 to 29.0 seconds, with a mean of 25.0 seconds, but the disappearance rates were lower (2.2 to 9.6 per cent, mean of 4.2 per cent) than in the patients without heart failure. The products of these two parameters, which ranged from 57.5 to 278.4 with a mean of 109.5, exceeded those in the patients with left-to-right shunts primarily because of the prolonged build-up times.

The curves in the 2 patients without shunts who had tricuspid regurgitation resembled those found in patients with left-to-right shunts. The build-up times were short, but the disappearance rates were low, and the products of these two parameters were in the same range as in the patients with shunts.

The relation between the pulmonary/systemic flow ratio, determined from the inhaled Kr^{85} test, and the build-up time disappearance rate product derived from the precordial dilution curve is plotted in figure 3. It is evident that only a rough estimate of the magnitude of the shunt was provided by the precordial dilution curve.

Discussion

The results of the application of the precordial scanning technic indicate that this method is simple and safe, and with few exceptions constitutes a reliable technic for the detection of left-to-right cardiac shunts. Although minute shunts may not be detected, it is notable that in 7 patients whose precordial curves were characteristic of left-to-right shunts the pulmonary/systemic flow ratios ranged between 1.2/1.0 and 1.5/1.0. Since the scintillation detector was focused over the right atrium and right ventricle, it would be

Table 2

Results of Precordial Scanning in Patients without Left-to-Right Shunts

Patient	Age (yr.)	Diagnosis	B. T. (sec.)	D. R. (% sec.)	B. T. X D. R.
A. T.	28	ASD (post-op)	11.0	5.0	55.0
N. D.	6	PS	5.0	12.0	60.0
J. K.	18	FM	7.0	9.4	65.8
C. L.	14	PS	8.0	8.5	68.0
D. M.	50	AI	8.0	8.8	70.4
J. F.	8	Coarct.	6.0	12.0	72.0
J. C.	22	Tet. of Fal.	13.0	5.7	74.1
T. S.	8	FM	5.0	15.0	75.0
D. W.	11	ASD (post-op)	6.5	12.0	78.0
W. N.	35	FM	7.0	11.9	83.6
B. B.	7	VSD (post-op)	5.0	18.0	90.0
G. G.	9	FM	5.0	19.0	95.0
G. G.	24	PS	10.0	9.7	97.0
R. O.	17	PS	9.0	12.0	108.0
B. W.	18	FM	10.0	12.0	120.0
		Rheumatic heart disease (without congestive heart failure)			
L. W.	40	MS, MI	14.0	4.2	58.8
E. B.	36	TI	10.0	6.0	60.0
E. M.	37	MS	9.0	7.1	63.9
J. M.	36	AS, AI	10.5	6.4	67.2
C. B.	22	AS	10.0	6.8	68.0
A. K.	37	AS	7.0	9.9	69.3
F. P.	7	MI	7.0	9.9	69.3
M. B.	16	AS	7.0	10.0	70.0
C. M.	7	AS	5.0	14.0	70.0
J. O.	17	AS	7.0	10.0	70.0
R. B.	15	AS	8.0	10.0	80.0
O. C.	15	MI	9.0	9.3	83.7
J. M.	23	AI	14.0	6.4	89.6
S. G.	36	MS	13.0	7.0	91.0
N. W.	63	AS	11.0	8.5	93.5
R. P.	20	MS	11.0	10.0	110.0
C. M.	45	AS	14.0	8.1	113.4
		Rheumatic heart disease (with congestive heart failure)			
B. B.	27	MI	25.0	2.3	57.5
L. M.	30	MI	27.0	2.2	59.4
B. D.	44	MI	24.0	3.1	74.4
W. L.	42	MS	20.0	3.9	78.0
C. S.	60	MS	29.0	9.6	278.4
		Rheumatic heart disease (with tricuspid insufficiency)			
E. B.	39	MS, TI	11.0	2.7	26.0
F. H.	52	MI, TI	13.0	2.0	29.7

Abbreviations: PS = Congenital pulmonic stenosis. FM = Functional murmur. Coarct. = Coaretation of aorta. Tet. of Fal. = Tetralogy of Fallot. MS = Mitral stenosis. MI = Mitral insufficiency. TI = Tricuspid insufficiency. AS = Aortic stenosis. AI = Aortic insufficiency. TI = Tricuspid insufficiency. B. T. = Build-up time. D. R. = Disappearance rate.

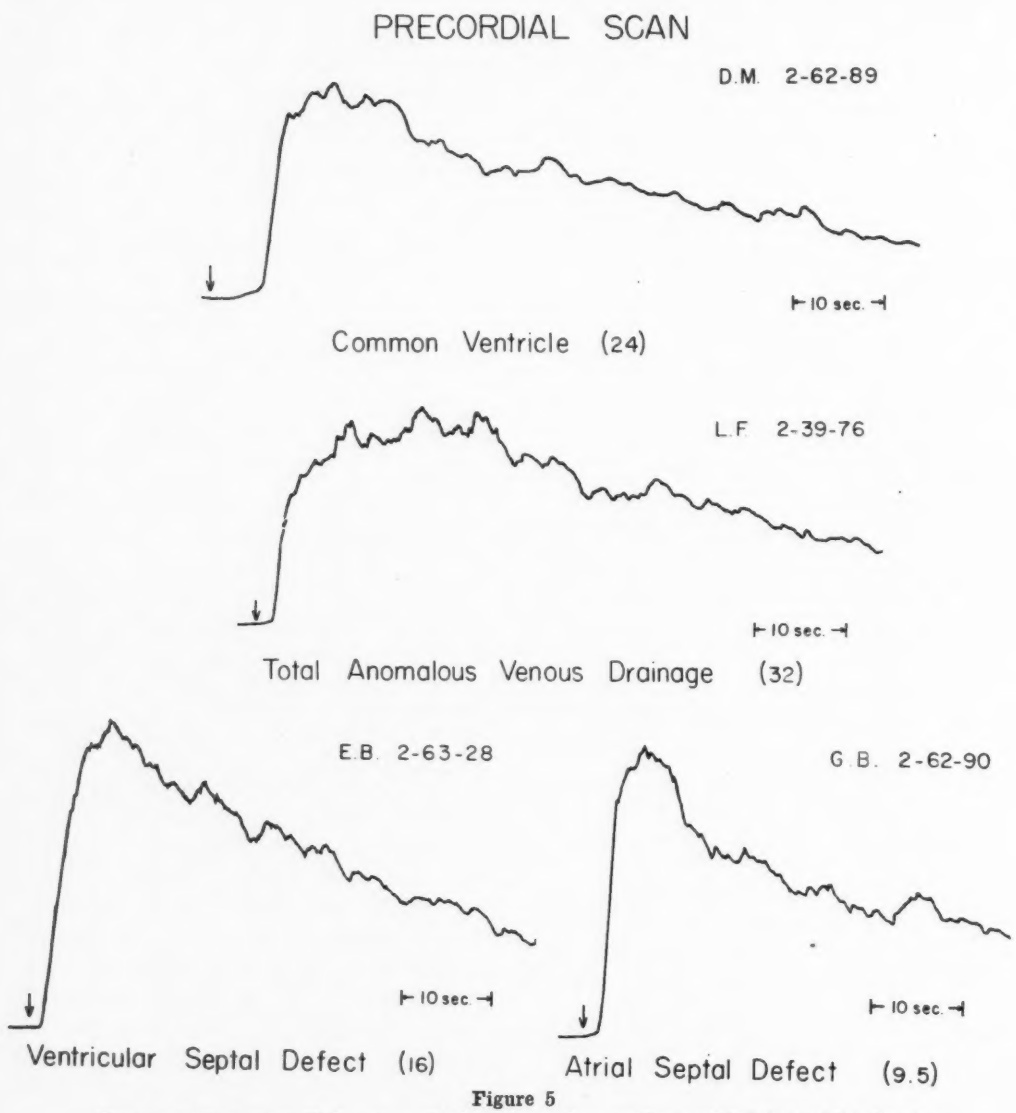

Figure 5

Representative precordial curves obtained from four patients with left-to-right shunts. In each instance the numbers in parentheses indicate the product of build-up time and disappearance rate.

anticipated that the method would be useful in detecting shunts that entered these two chambers. In patients with left-to-right shunts entering the pulmonary artery the isotope does not recirculate abnormally through the right side of the heart, and the precordial curves may not be distinctly abnormal. Placement of the detector over the second left intercostal space in a patient with a patent ductus arteriosus, however, yielded an abnormal curve. It would appear likely that this position of the detector will make the recognition of the majority of these lesions possible.

The product of the build-up time and the

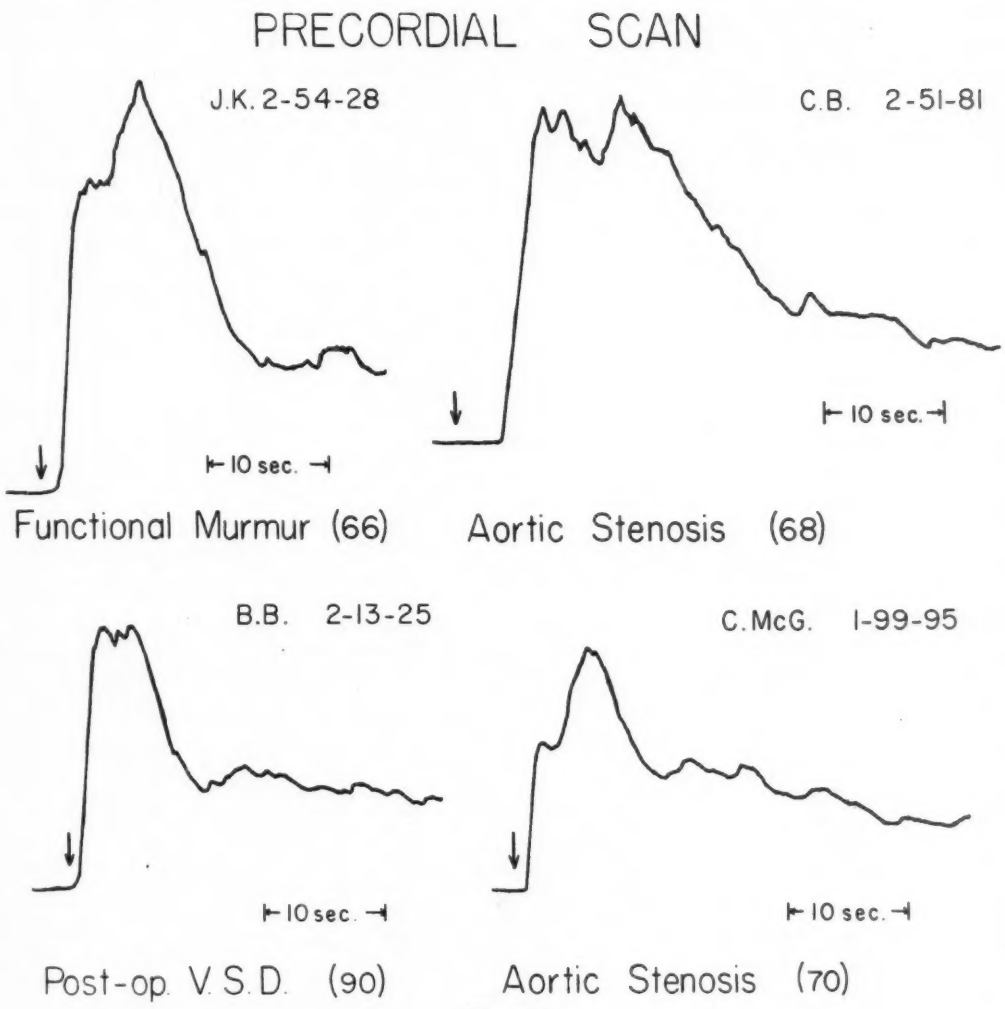

Figure 6

Representative precordial curves obtained from patients without shunts. In each instance the numbers in parentheses indicate the product of build-up time and disappearance rate.

disappearance rate was found to be useful in analyzing the precordial curves, since the former parameter is a function of the circulation time while the latter is related to the rate of clearance of isotope from the central circulation. The specific values obtained in any given patient of course depend on the specific characteristics of the instruments employed and differ, for example, if a different response time of the count-rate meter is utilized. In most patients with heart failure, as well as in those with left-to-right shunts, the disappearance is prolonged; but the prolonged circulation time in congestive heart failure elevates the build-up time and therefore raises the product of build-up time and disappearance rate. In patients without left-to-right shunts or heart failure, the build-up time is as short as in the patients with left-to-right shunts, but the disappearance rates in

the two groups differ. When severe tricuspid regurgitation is present, or when overt heart failure complicates a left-to-right shunt, the results of precordial scanning are probably less accurate.

One of the advantages of the technic employed in the present study is the reduced radiation hazard to the patient provided by the use of I^{131}-labeled Diodrast. Furthermore, the use of larger, more sensitive scintillation detectors will in the future permit further reduction in the dosage of isotope employed.

Precordial scanning promises to be of greatest value in the study of patients who have systolic murmurs, but in whom the presence or absence of a left-to-right shunt cannot be determined with certainty on the basis of the usual clinical examinations. Thus, the technic may be useful in screening patients encountered in outpatient clinics, induction centers, or in any setting in which a large number of individuals are examined. A precordial dilution curve that suggests the presence of a left-to-right shunt should be followed by a complete cardiac catheterization in order to confirm the presence of the shunt, to localize it, and to establish its magnitude.

Precordial scanning has also found application in the study of patients in the early postoperative period following correction of lesions responsible for left-to-right shunts. When complications, such as heart failure and tachycardia, occur during this period, the possibility of a persistent or reopened defect should be considered. Auscultatory findings are of little value at this time because of the many adventitious sounds that are often present. Cardiac catheterization is ordinarily contraindicated in such an acutely ill patient, but precordial scanning has, in several instances, clarified the problem by clearly indicating either the presence or absence of a persistent left-to-right shunt.

Summary

A precordial scanning technic and its application in the detection of left-to-right cardiac shunts in 75 patients are described. I^{131}-labeled Diodrast was injected into an antecubital vein, its concentration in the central circulation was metered by means of a scintillation detector, and the time-concentration curve were recorded directly. In patients with left-to-right shunts these curves were modified in a characteristic fashion; the build-up time was normal, but the disappearance of isotope from the central circulation was slow. The product of the build-up time and disappearance rate was generally lower than in patients without cardiac shunts. The clinical value of this simple technic in detecting or excluding the presence of left-to-right shunts is discussed.

Acknowledgment

The advice of Drs. R. Gorlin and I. Turner in setting up this technic is gratefully acknowledged.

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From this experiment we see how greatly the velocity of the water is retarded in passing thro' the several branchings of the arteries, nothwithstanding the sum of the areas of their transverse section is considerably greater than that of the *aorta.* For although the velocity of the blood at its first entrance into the *aorta,* depends on the proportion the area of its orifice bears to the quantity thrown into it at each *systole,* and also on the number of those *systoles* in a given time: yet the real force of the blood in the arteries, depends on the proportion, which the quantity of blood thrown out of the left ventricle in a given time, bears to the quantity which can pass thro' the capillary arteries into the veins, in that time. But the resistance which the blood meets with in those capillary passages, may be greatly varied, either by the different degrees of viscidity or fluidity of the blood, or by the several degrees of constriction or relaxation of those fine vessels. And as the state of the blood or blood-vessels is in these respects continually varying from divers causes, as motion, rest, food, evacuations, heat, cold, etc., so as probably never to be exactly the same any two minutes, during the whole life of an animal; so the blood in passing thro' the muscular, the membranous, and other parts of the animal, must be carried on with innumerable different degrees of velocity, and consequently in different quantities, thro' dissimilar parts.—STEPHEN HALES, B.D., F.R.S. *Haemastatics,* Vol. II, London, 1733.

An Electrocardiographic Pattern Associated with Mitral Valve Deformity in Marfan's Syndrome

By DORRANCE BOWERS, M.D.

IN A RECENT REVIEW[1] of the electrocardiograms of 55 patients with Marfan's syndrome, a pattern of S-T depression or T-wave inversion in leads II, III, and aV_F* was observed in 7 patients. Subsequently, it was found that in 2 of these 7 patients (previously coded[1] as M.Mc.G. no. 45 and as W.H. no. 50), deformity of the mitral valve had been demonstrated at the time of necropsy examination. This observation prompted a review of the electrocardiographic findings in other patients with Marfan's syndrome and proved deformity of the mitral valve. It has been readily possible to collect from recent medical literature 3 additional examples of mitral valve deformity in patients with Marfan's syndrome. In these 3 patients also, there were abnormalities of repolarization in electrocardiographic leads II, III, and aV_F*. It is the purpose of this collective review to document briefly this association between electrocardiographic and anatomic abnormalities.

Report of Cases

Case 1

(Previously coded[1] as M.McG. no. 45, this patient was illustrated by McKusick in figure 1*c* in the first edition[2a] of his monograph and in figure 4*e* in the second edition;[2b] his code number A92675.)

This white girl was 10 years old at the time of her death at the Hospital for Sick Children[3] in Toronto. She presented the following stigmata of Marfan's syndrome: bilateral ectopia lentium, scoliosis, and pectus excavatum. Electrocardiograms made on July 18, 1951, when the patient was 5 years of age, and on November 9, 1956, shortly before her death, are presented in figure 1. At necropsy examination the mitral valve was found to have 3 cusps and abnormally short chordae tendineae.

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*When lead aV_F was not recorded, the author has assumed that the pattern of repolarization in lead aV_F would have been similar to that in leads II and III.

Case 2

(Previously coded[1] as W. H. no. 50.) This white man with Marfan's syndrome was studied at the Toronto General Hospital.[4] An electrocardiogram made on August 30, 1954, when the patient was 19 years old showed atrial fibrillation and S-T depression and T-wave inversion in leads II, III, and aV_F. At the time of necropsy examination it was observed that the endocardium of the left atrium and over the anterior leaflet of the mitral valve was abnormally thick and yellow; the mitral valve orifice measured 17 cm. in circumference (the normal value for this measurement is 7.5 cm.)

Case 3

(This patient was reported[5] from the United States Naval Hospital, Bethesda, Maryland, by Drs. Russell Miller, Jr. and R. J. Pearson, Jr.)

This Negro patient was 27 years old at the time of her examination. She had bilateral ectopia lentium, pectus carinatum, kyphoscoliosis, and arachnodactyly. Her electrocardiogram (presented in their figure 4 by Miller and Pearson[5]), in addition to other abnormalities, shows S-T depression and T-wave inversion in leads II, III, and aV_F. In this patient, at the time of necropsy examination, it was observed that the anterior mitral cusp was thickened, calcified, and studded with vegetations; the chordae tendineae were thickened, and one of the chordae had ruptured close to its attachment to the valve leaflet.

Case 4

(This patient was reported[6] from the Jewish Hospital, Louisville, Kentucky, by Dr. Abraham Gordon and coded as no. 32436.)

This patient was a 24-year-old white man at the time of his death. The lens had been surgically removed from his right eye; the left lens was dislocated upwards. In addition, he had a moderate pigeon-breast deformity. There was an extensive family history of Marfan's syndrome. An electrocardiogram (kindly supplied[7] to the author by Dr. Gordon) made on November 29, 1946, is reproduced in figure 2. At the time of necropsy examination the superior half of the mitral valve proved to be densely adherent to the endocardial surface of the left ventricle anteriorly, and at the upper margin of the valve bony spicules protruded into the ventricular cavity. On microscopic examination the mitral valve proved to be hyalinized and acellular.

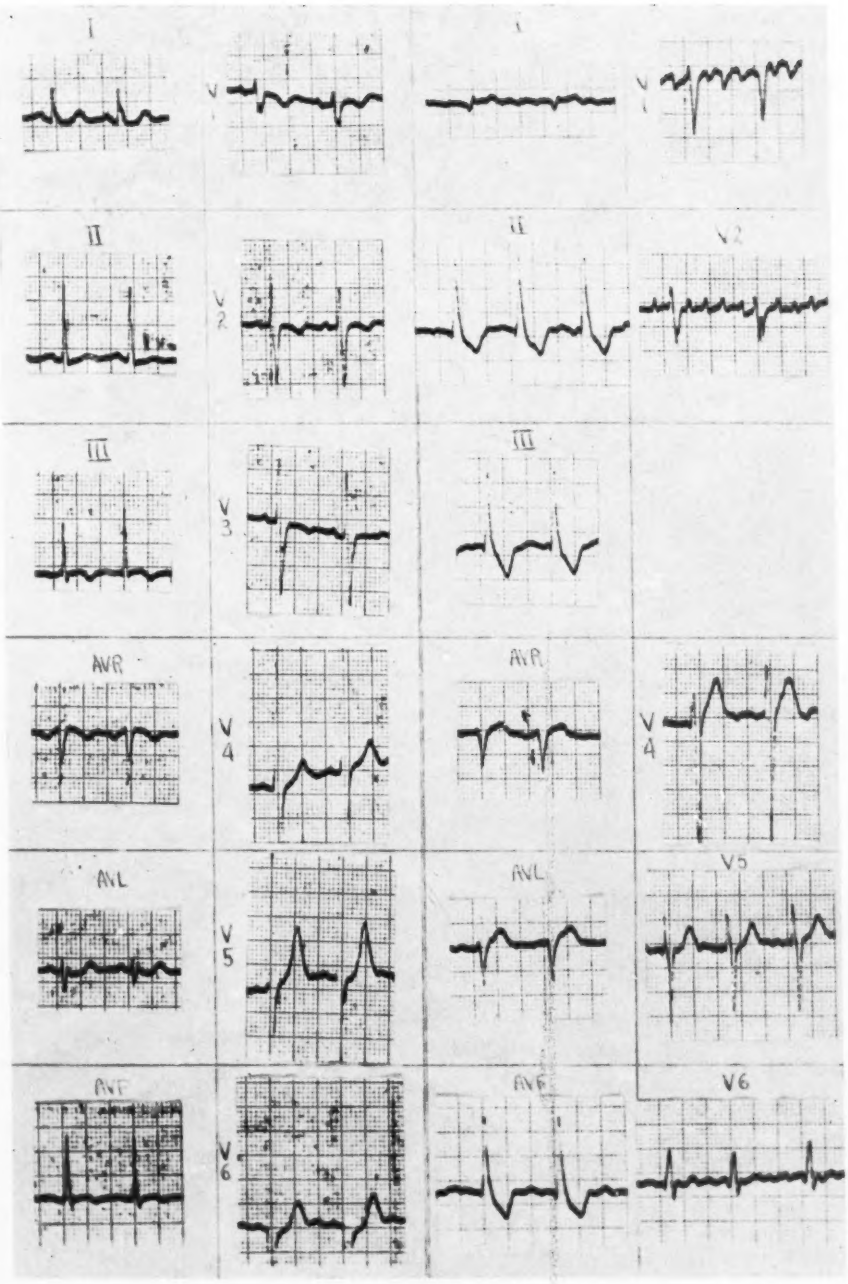

Figure 1

Electrocardiograms from case 1. The tracing on the left was made on July 18, 1951. Note the sinus rhythm, the S-T depression in lead II, and the inversion of the T waves in leads III and aV_F. The tracing on the right was made on November 9, 1956. Note the atrial fibrillation and the S-T and T-wave abnormalities in leads II, III, and aV_F.

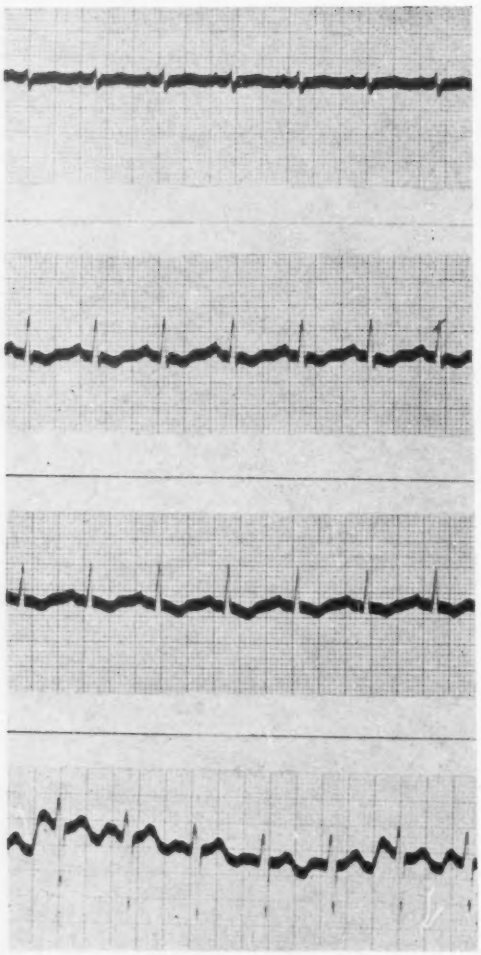

Figure 2

Electrocardiogram (leads I-IV) from case 4. This electrocardiogram was made on November 29, 1946. Note the S-T depression and T-wave inversion in leads II and III.

Case 5

(This patient was reported from Johns Hopkins Hospital, Baltimore, Maryland, by Dr. Victor McKusick. She was coded as M.E.C. (J.H.H. A98174) and described on page 60 in the first edition[2a] of his monograph, and on page 91 in the second edition.[2b] She has also been mentioned in 2 other reports.[8, 9])

This patient was a 15-year-old white girl at the time of her death. She was tall and slender, and had bilateral ectopia lentium and scoliosis. Her electrocardiogram showed changes in the ST-T complexes in leads II and III interpreted as "right ventricular strain pattern."* At the time of necropsy examination the mitral valve was found to have 5 cusps with nodular thickening along the line of closure. On microscopic examination this area showed basophilic degeneration.

Discussion

Deformity of the mitral valve in a patient with Marfan's syndrome was first recorded by Salle[10] in 1912. Subsequently, Traisman and Johnson[11] and McKusick[2] have emphasized that mitral valve abnormalities occur not infrequently in patients with Marfan's syndrome. In some of these patients the mitral valve deformity is probably an intrinsic part of the genetically determined abnormality of connective tissues; in others, the mitral valve abnormalities appear to have resulted from complicating rheumatic fever or subacute bacterial endocarditis. Since both rheumatic fever and subacute bacterial endocarditis[12] may pass unrecognized during life, one can only speculate, at the present time, on the relative importance of genetic and environmental factors in the causation of the mitral valve deformities in these patients.

The pathogenesis of the S-T and T-wave abnormalities in the electrocardiograms of these 5 patients is also not clear. Barnes[13, 14] (prior to the introduction of unipolar electrocardiographic leads) noted that S-T depression or T-wave inversion in standard leads II and III was often associated with right ventricular strain or with the administration of digitalis. Presumably these same factors were operating in the patients described in this report; but again, one can only speculate on the relative importance of right ventricular hypertrophy and administration of digitalis in the genesis of the electrocardiographic abnormalities in these 5 patients.

It is of interest that, in this series of patients, the significant clinical cardiovascular abnormality was mitral valve insufficiency. In a review[15] of the electrocardiograms of 23 patients with "pure mitral insufficiency," S-T and T-wave abnormalities in leads II, III, and

*It is the author's presumption that this pattern consisted of S-T depression or T-wave inversion.

aV_F were not mentioned. Thus, the electrocardiogram may serve to distinguish between the mitral valve insufficiency of rheumatic heart disease and of Marfan's syndrome.

In recent years aortic valvular insufficiency in Marfan's syndrome has attracted wide interest.[16] The electrocardiographic pattern of left ventricular hypertrophy is to be expected in such patients.[1] In a patient with Marfan's syndrome, S-T depression or T-wave inversion in electrocardiographic leads II, III, and aV_F should arouse suspicion of mitral valve deformity.

Summary

A collected series of 5 patients with Marfan's syndrome is reported in whom S-T depression and T-wave inversion in electrocardiographic leads II, III, and aV_F were associated with necropsy-proved deformity of the mitral valve.

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In so complicated a subject as the animal body, all things are wisely adjusted in number, weight and measure, yet with such complex circumstances as require many *data* from experiments, whereon to found just calculations: but though many of the following calculations are founded only on such inaccurate mensurations as the nature of the subject would allow of; yet may we thence fairly draw many rational deductions in relation to the animal oeconomy.—Stephen Hales, B.D., F.R.S. *Haemastatics*. Preface, Ed. 3.

Separated Renal Functions in Patients with Renal Arterial Disease, Pyelonephritis, and Essential Hypertension

By HARRIET P. DUSTAN, M.D., EUGENE F. POUTASSE, M.D., A. C. CORCORAN, M.D., AND IRVINE H. PAGE, M.D.

ATHEROSCLEROSIS, fibrous proliferation, or primary dissecting aneurysm of main renal arteries or their primary branches may cause hypertension and can alter renal blood flow, filtration rate, sodium excretion, and water reabsorption.[1, 2] Mechanisms of the changes in sodium and water transport are not fully understood; they may include decreases in intrarenal arterial pressure, glomerular filtration rate, distribution of peritubular blood, and, if renal atrophy is present, some change in tubular function. In dogs, partial constriction of one main renal artery provokes the excretion of urine of diminished volume and sodium concentration, and increased osmolality.[3, 4] However, if the number of functioning nephrons is decreased by complete occlusion of primary branches of the main renal artery or by unilateral parenchymal disease, urine volume, filtration rate, and osmolality are, alike, decreased.[5-7] These experiments indicate that differences in renal functional patterns would be found in hypertensive patients with occlusive renal artery disease depending upon whether the lesion involves the main renal artery, some of its primary branches, or is associated with pyelonephritis.

This report describes specific functions of individual kidneys of hypertensive patients with renal artery disease and compares them with those found in pyelonephritis and essential hypertension.

Methods

Separated function tests were carried out in 45 hypertensive patients. These were divided into groups on bases of clinical history, results of intravenous urography and renal angiography; this last test was performed in *all*. Ten were considered to have essential hypertension; 8, pyelonephritis; 10, occlusive disease of one main renal artery; 8, occlusive disease of both main renal arteries; and 9, lesions of one or more primary arterial branches which in 6 had resulted in segmental renal infarction.

Tests were performed in the afternoon during mannitol diuresis without dehydration; vasopressin infusion substituted for fluid deprivation as the stimulus for free water reabsorption. No attempt was made to regulate fluid intake during the few days prior to the test. The patients were put to bed at least 2 hours before the test and were given routine preoperative medication of a barbiturate, morphine and atropine. Urine was collected from one kidney through an occluding ureteral catheter passed approximately 4 cm. up from the ureterovesical junction and from the other continuously through the water intake valve of the cystoscope. To insure that the ureter was completely occluded, indigo carmine was injected into the catheter; if the dye did not appear in the bladder urine, the occlusion was considered complete and urine collections were carried out over 2 15-minute periods. During the test, rates of urine flow were observed carefully; if at any time flow from the catheter decreased and that from the bladder increased, collections were interrupted, ureteral occlusion rechecked with indigo carmine and, if found to be defective, the catheter was reset. In those patients with urographic or angiographic suggestion of disparities in renal functions, the side suspected of lower urine volume was catheterized to avoid artifacts incident to collecting small urine volumes from the bladder. The procedure has been previously described in more detail.[8]

To measure renal functions, solutions of mannitol and vasopressin, with or without paraaminohippurate (PAH) were given intravenously. The priming solution delivered 20 mOsm of mannitol per liter of extracellular fluid (estimated as 20 per cent of the body weight) and 100 mU of vasopressin. The sustaining solution delivered 3 mOsm of mannitol and 1.5 mU of vasopressin per minute. PAH was administered in amounts sufficient to maintain plasma concentrations of 2 to 3 mg. per cent. C_{PAH} measurements were omitted in patients receiving sulfonamides.

Among the functions measured were renal plasma flow (RPF)—from the plasma clearance of PAH, glomerular filtration rate (GFR)—mannitol

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clearance multiplied by 1.1, filtration fraction (FF), urine flow (V), urine osmolality (U_{Osm}), osmolal clearance (C_{Osm}), urine sodium concentration (U_{Na}), and the excreted fraction of the filtered sodium load (EF_{Na}). Analytical methods have been previously described.[9, 10]

Results

Values for left kidneys in essential hypertensive subjects appear in the odd-numbered columns and for the right kidneys in the even-numbered columns of table 1. Values measured in the affected or more-affected kidneys of other groups are listed in the even-numbered columns.

Essential Hypertension

Absolute rates of RPF and GFR were depressed and FF was elevated. Differences between the two sides were usually within the accuracy of the method used, i.e., within 10 per cent. Differences in V ranged from 0.03 to 0.4 ml. per minute. The maximum difference of 0.4 ml. per minute indicated that in only 1 patient was V from one side as much as 10 per cent less than that from the other. Similar consistency in the values between the two sides obtained for RPF, GFR, FF, U_{Osm}, and C_{Osm}. Differences in U_{Na} were less than 10 per cent on the two sides except in patient no. 9 in whom a 15 per cent difference was found. At low values of EF_{Na} disparities ranged from 14 to 37 per cent (patients nos. 2, 3, 9); at higher levels, disparities did not exceed 10 per cent.

Pyelonephritis

Disparities were observed in V, RPF, and GFR. In the 6 patients in whom RPF was measured, FF was higher on the more affected side; U_{Osm} was lower on the more affected side in 4 of the 8 and C_{Osm} was less in all. U_{Na} was nearly the same on the two sides; differences in EF_{Na} were insignificant except in patients nos. 17 and 18, in whom it was 25 per cent and 26 per cent higher on the more affected side.

Unilateral Renal Artery Disease

Nine of these 10 patients showed similar functional patterns. On the *unaffected side*, by reference to average normal values, RPF was slightly depressed in 7 of the 8 patients in whom it was measured; GFR was normal or increased; FF was increased in all. On the *affected* side, V was depressed and this depression was out of proportion to decreases of RPF and GFR; FF was strikingly less. In all of these 9 patients, U_{Na} was much lower on the side of the lesion; the least depression, when compared with the opposite side, was 14 per cent and the maximum depression was 88 per cent. Without exception EF_{Na} was strikingly reduced and U_{Osm} increased.

The remaining patient of this group, no. 28, a 9-year-old girl with fibrous intimal proliferation of the right main renal artery, did not show the distinctive renal functional characteristics detailed above. Urine volume, RPF, and GFR were lower on the affected side, but FF, U_{Na}, U_{Osm}, and EF_{Na} were the same on the two sides.

Bilateral Main Renal Artery Disease

Differences in V, RPF, and GFR were found between the two sides. In 3, FF was significantly lower on the side of the lower GFR. Values for U_{Osm} were disparate in 7; in 5 it was higher on the side of the lower GFR (as observed in patients with unilateral artery disease) but in 2 patients with severe functional loss (GFR, respectively 1.3 and 4 ml. per minute) the lesser U_{Osm} was on the side of the lower GFR; C_{Osm} was lower on the more affected side. Values for U_{Na} were dissimilar in all patients; in 6, the lower U_{Na} was found on the side of the lower GFR, while in 2 it was higher on that side. Differences in EF_{Na} paralleled the differences in U_{Na}.

Lesions of Primary Arterial Branches

Branch Lesions. Six patients had unilateral lesions and 2, bilateral (nos. 44 and 45). Renal functions resembled those found in pyelonephritis, except in patient no. 44, in whom the similarities of functions on the two sides can be explained by the presence of bilateral renal infarcts that happened to result in the equal depressions of V, RPF, and GFR. In the remaining patients, significant depressions on the affected or more affected side were observed. For the rest of the functions values

Table 1

Separate Renal Functions in Patients with Essential Hypertension, Pyelonephritis, and Occlusive Renal Artery Disease

Column	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Patient no.	V		RPF		GFR		FF		U_{Osm}		C_{Osm}		U_{Na}		EF_{Na}	
	ml./min./1.73 M.²								mOsm/Kg. H_2O		ml./min./1.73 M.²		mEq./L.		%	
	Essential hypertension															
1	3.90	3.87	183	182	44	39	0.24	0.21	442	449	5.70	5.76	89	89	5.77	6.42
2	3.81	3.41	166	151	45	43	0.27	0.28	372	376	4.86	4.41	51	46	3.50	3.01
3	2.81	2.72	103	106	30	33	0.29	0.31	386	377	3.65	3.46	23	24	1.30	1.89
4	6.07	5.81	178	162	47	43	0.27	0.27	324	325	6.60	6.32	64	63	6.22	6.26
5	3.18	3.33	68	73	22	23	0.32	0.32	360	356	3.73	3.87	57	55	6.61	6.29
6	3.73	3.88	194	190	49	46	0.25	0.25	451	424	5.71	5.59	65	62	3.52	3.63
7	5.08	5.05	250	279	56	53	0.23	0.21	365	360	6.57	6.44	77	81	5.17	4.79
8	3.58	3.30	96	91	31	28	0.32	0.31	332	338	4.14	3.87	76	77	6.79	7.16
9	3.57	3.85	206	199	67	62	0.33	0.31	489	490	5.84	6.30	54	64	2.16	2.97
10	5.19	4.90	152	150	41	39	0.28	0.28	301	302	5.04	4.78	83	82	14.9	15.1
	Pyelonephritis															
11	5.16	1.94	218	76	48	18	0.22	0.25	416	419	7.19	2.72	66	65	5.80	5.51
12	4.47	2.68			41	24			396	398	6.10	3.64	67	73	6.65	6.67
13	11.90	3.48	316	83	86	24	0.27	0.29	373	366	14.7	4.23	100	100	9.74	10.2
14	12.40	1.76	152	22	59	8	0.39	0.40	312	302	12.8	1.76	98	98	15.0	15.4
15	8.98	2.97	211	66	73	24	0.35	0.36	370	329	11.0	3.33	93	91	8.12	8.88
16	6.04	.74	330	30	51	6	0.15	0.21	481	414	9.90	1.04	82	88	7.26	8.06
17	6.07	3.33			70	32			462	405	9.41	4.53	68	71	4.51	5.65
18	4.54	1.75	291	96	56	20	0.19	0.21	466	433	6.93	2.48	41	46	2.53	3.19
	Unilateral main renal artery disease															
19	3.27	2.18	193	177	59	50	0.31	0.28	494	562	5.56	4.21	72	47	2.90	1.52
20	3.85	2.01	268	166	69	42	0.26	0.25	462	517	7.85	3.65	71	57	3.60	1.94
21	7.60	0.99	266	56	71	12	0.27	0.21	412	422	10.7	1.43	75	32	6.69	2.15
22	5.04	2.11	236	184	71	41	0.30	0.22	413	443	7.06	3.17	64	12	3.36	.40
23	7.91	2.66	169	120	89	48	0.53	0.40	337	437	9.17	4.02	55	21	3.50	.85
24	10.60	1.90	236	123	75	33	0.32	0.28	345	488	12.4	3.16	91	39	9.64	.99
25	7.62	1.52	449	267	92	43	0.20	0.16	421	624	10.9	3.24	88	10	5.06	.26
26	9.34	0.60			81	15			254	489	7.98	.98	55	7	4.68	.20
27	6.25	3.03	238	238	62	53	0.26	0.22	414	497	8.58	5.00	86	33	6.45	1.43
28	3.87	3.07	277	240	73	62	0.26	0.26	521	520	6.61	5.24	20	18	.82	.70
	Bilateral main renal artery disease															
29	7.47	1.26	302	133	87	31	0.29	0.23	383	562	9.81	2.43	71	29	4.43	.86
30	2.13	0.21	127	8	21	1.4	0.15	0.16	360	338	2.60	.24	31	47	2.75	5.33
31	3.22	2.75	229	171	56	46	0.25	0.27	505	521	5.45	4.80	65	81	2.83	2.59
32	3.64	2.58			61	49										
33	6.47															

	Bilateral main renal artery																
29	7.47	1.26	302	133	87	31	0.29	0.25			2.60	.24	31	47			
30	2.13	0.31	127	8	21	1.4	0.15	0.16	360	338							
31	3.22	2.75	229	171	56	46	0.25	0.27	505	521	5.45	4.80	65	81	2.83	3.59	
32	3.64	2.58			61	49			442	454	5.60	4.09	56	48	2.52	1.95	
33	6.47	5.56	147	117	27	24	0.18	0.21	270	273	5.77	5.01	58	48	10.8	8.73	
34	13.7	2.90	211	124	70	32	0.33	0.26	259	354	11.8	3.43	69	37	10.1	2.63	
35	3.34	.42	132	21	36	4.4	0.27	0.19	440	403	4.81	.58	48	28	3.65	2.23	
36	10.5	5.33	458	352	75	55	0.16	0.16	379	447	13.1	7.86	82	65	8.84	4.84	
	Branch lesion																
37	9.29	4.21	199	112	70	32	0.35	0.29	327	339	10.0	4.75	102	99	9.38	8.91	
38	9.82	7.37	250	221	83	67	0.33	0.30	320	331	10.9	8.54	71	69	5.96	5.36	
39	4.89	3.57	178	118	52	34	0.29	0.29	473	450	7.62	5.29	72	79	4.73	5.76	
40	7.44	2.38	506	163	89	31	0.18	0.19	404	403	10.0	3.20	59	56	3.70	3.94	
41	6.85	3.23	249	117	62	27	0.25	0.23	381	377	8.99	4.19	72	70	5.66	5.97	
42	5.90	3.09			57	30			389	384	7.67	3.97	62	61	4.82	4.68	
43	10.4	7.04	244	146	76	47	0.31	0.32	314	304	11.0	7.15	75	76	7.54	8.30	
44	6.03	5.93	283	263	65	62	0.23	0.24	440	419	8.92	8.34	77	79	5.60	5.92	
45	3.19	2.34	210	146	42	31	0.33	0.26	450	441	4.92	3.54	23	25	1.32	1.45	

V, urine flow; RPF, renal plasma flow, GRF, glomerular filtration rate; FF, filtration fraction; U_{Osm}, urine osmolality; C_{Osm}, osmolal clearance; U_{Na}, urine sodium concentration; EF_{Na}, excreted fraction of filtered sodium load.

For essential hypertensive subjects values for left kidneys appear in odd-numbered columns and for right kidneys in even-numbered columns; for the other groups values for the affected and more-affected kidneys appear in even-numbered columns.

of FF were disparate in 3, U_{Osm} was practically equal; U_{Na} and EF_{Na} were not different except in 1 patient (no. 39) in whom U_{Na} was 10 per cent and EF_{Na} 22 per cent higher on the affected side.

Discussion

Procedure

The method of collection employed in these studies involves collecting urine from one kidney through an occluding ureteral catheter and from the other via bladder. This technic has been criticized on several counts. The first is that ureteral occlusion may not be complete throughout the test, even though it is shown to be complete at the beginning. Thus, urine leakage would go undetected, since it would be mixed with urine from the opposite kidney. Further, the possibility has been suggested that ureteral catheterization might, of itself, modify renal function.[11] If either of these situations had regularly obtained, significant disparities should have been found in patients with essential hypertension, for urine flow from the catheterized side would have always been less. This was not the case, and minor decreases of function that were observed were not necessarily on the side of ureteral catheterization. It should be emphasized that, although the catheter is seated firmly in the ureter, there is no obstruction to free urine flow. Reflex depression of renal function arising from ureteral manipulation, while possible, has not been a problem.[12] Yendt et al.[13] have suggested that urine from the uncatheterized side may lose sodium through the bladder wall and this loss would vitiate the results of the test. This does not seem to be the case as shown by the similarities of U_{Na} on the two sides in patients with essential hypertension, pyelonephritis, and branch lesions. That this has not been a problem is, perhaps, because the bladder is constantly drained and urine is not allowed to remain in it.

Further evidence for reliability appears in table 2. In this patient, tests were performed 3 days apart. At the first test the right ureter was catheterized; because urine flow from this side was unexpectedly higher, the test was

Table 2

Results of Function Tests of the Individual Kidneys of One Patient Done on Two Different Days and with Alternating the Ureteral Catheter

V		RPF		GFR		FF		U_{OSM}		U_{Na}	
		ml./min./1.73M.^{2}						mOsm/Kg. H_2O		mEq./L.	
L	R	L	R	L	R			L	R	L	R
	5-6-59	Right ureter catheterized									
2.69	3.94	175	249	41	56	0.23	0.22	440	403	55	58
	5-6-59*	Left ureter catheterized									
2.19	3.10	173	229	33	49	0.19	0.22	588	549	42	41

*After 2 days of chlorothiazide.
See table 1 for key to abbreviations.

repeated and the left ureter was catheterized. Again the higher rate of urine flow was from the right kidney. The depression of GFR observed during the second test was due to 2 days of chlorothiazide treatment.[14]

In previous studies of separate renal functions[11, 13, 15–17] specimens were collected by bilateral ureteral catheterization; to check for leakage the bladder was also catheterized. One difficulty with bilateral catheterization is the doubled hazard of leakage during ureteral peristalsis. Another is that at low rates of urine flow significant leakage could occur but the volume (say, 3 ml. in 30 minutes) could be so small as to escape drainage via the bladder catheter. By means of this procedure, the bladder is drained at the end of the collection period and by analysis an attempt is made to determine the kidney from which this urine originated. However, retention of urine in the bladder could allow for transfer of electrolytes through the bladder mucosa[13, 20] and so change the composition of the urine that it would not be recognizable as belonging to either kidney.

Obviously, neither method is ideal because of the possibility of escape of urine around the catheters into the bladder. Our experience suggests that unilateral ureteral catheterization gives results as valid as does bilateral catheterization.

Essential Hypertension

The finding of similarities of functions of the two kidneys in patients with essential hypertension confirms and extends earlier observations of Chasis and Redisch.[15] It is not in accord with the recent studies of Baldwin et al.,[17] which showed disparities of separate renal functions in 40 of 50 patients considered to have essential hypertension but not examined by renal angiography. Accordingly, they have concluded that significant disparities in functions of the two kidneys develop in the course of essential hypertension. This conclusion was based on comparison of these results with those of 21 normotensive subjects.[18] In the normotensive group, arbitrary limits of normality were established, and interpretation of data from the hypertensive group was based on these limits. When our data were analyzed by the same criteria, we found no significant disparities as concerned RPF, GFR, and U_{Osm}. V was significantly different in patient no. 2, FF in nos. 1 and 7; U_{Na} in no. 9, and EF_{Na} in nos. 2, 3, 9. The reason that the results of Baldwin et al. are different from those of Chasis and Redisch,[15] those of Connor et al.,[11] and those reported here is not apparent. It seems unlikely that four fifths of a group of hypertensive patients would suffer from clinically inapparent renal lesions. The fact that our studies were performed during mannitol diuresis is not an explanation; this could, however, obscure differences in sodium and water excretions but not in hemodynamic functions.

Pyelonephritis and Lesions of a Branch of the Main Renal Artery

The functional patterns found in patients with pyelonephritis and branch lesions were

similar, which suggests a common mechanism. As would be expected RPF and GFR were lower on the affected or more-affected side, except in patient no. 44, who had bilateral renal infarcts. In each instance changes in V were directly proportional to changes of GFR, and this is reflected in the tendency of U_{Osm} to be similar on the two sides. Slightly lower values for U_{Osm} were found on the more-affected side in 4 pyelonephritic patients. U_{Na} on the two sides was practically equal and only in 2 patients (nos. 17 and 39) was EF_{Na} considered to be significantly different.

The disparities in renal functions observed in these diagnostic groups suggest a quantitative decrease in numbers of nephrons but without a qualitative change in the function of those remaining. As concerns the findings in pyelonephritis, they are in accord with those of Michie et al.[16] whose studies led them to conclude, "in chronic pyelonephritis complete loss of nephron function predominates over specific impairment of glomerular and tubular function."

The experimental counterparts of these renal lesions are unilateral pyelonephritis and segmental ischemia in dogs as studied by Bricker et al.,[7] Blake[5] and Klapproth et al.[6] In each situation, function tests indicated a decrease in numbers of functioning nephrons with a supranormal GFR in the remaining nephrons, as evidenced by increased GFR/Tm_{PAH} and $GFR/Tm_{glucose}$ of the experimental kidney. Constant findings, also, were increased C_{Osm}/GFR and a lower U_{Osm}. In our clinical studies, U_{Osm} was not constantly decreased in the poorer functioning kidney, nor was C_{Osm}/GFR greater. Since we did not measure $Tm/_{PAH}$ or $Tm/_{glucose}$, we have no data concerning the magnitude of GFR in the residual nephrons. Perhaps the fact that mannitol was the major urinary solute obscured differences that might have been observed under another condition, such as water diuresis.

Main Renal Artery Lesions

In 9 of the 10 patients with unilateral occlusive disease of a main renal artery, disparities in renal functions were similar to those produced in dogs by narrowing one renal artery.[3, 4] In both species, the affected kidney excretes urine of smaller volume, higher osmolality and lower sodium concentration than its mate. The lower U_{Na} results from an enhanced sodium reabsorption as evidenced by the small amount of the filtered sodium that is excreted (EF_{Na}). This enhancement of sodium reabsorption on the affected side would, as Berliner et al. postulate,[19] increase the tonicity of the medullary interstitial fluid and promote water reabsorption. Accordingly urine flow would not be directly dependent on GFR, as seen in patients with pyelonephritis or branch arterial lesions, but would be depressed out of proportion to depressions of GFR. The fact that U_{Osm} was not greatly increased on the affected side is probably due to the mannitol diuresis with its augmented natriuresis and low urine urea concentration.[20] This would impair sodium reabsorption, diminish the effectiveness of urinary urea in the concentrating mechanism[21] and thus, mask that kidney's tendency for enhanced water reabsorption.

Patient no. 28 did not have the renal functional changes that would have been expected to result from renal artery stenosis. A 15 per cent reduction in GFR on the affected side was not accompanied by a reduction in U_{Na}. One might assume that the decrease in GFR and filtered sodium load was not great enough, in the presence of mannitol diuresis, to result in greater sodium reabsorption. However, in one other patient (no. 19) a 15 per cent reduction in GFR on the affected side was associated with a 35 per cent reduction in U_{Na}. That sodium reabsorption is affected by some factor other than the filtered sodium load is suggested by these findings and by the observation in patients with bilateral main renal artery lesions that the lower U_{Na} is not always on the side of the lower GFR.

Selkurt[22] has suggested that some hemodynamic function is partly responsible for the rate of sodium excretion. He studied renal hemodynamic functions and sodium excretion of dogs in which one kidney was perfused at

high or low arterial pressure levels, with or without a pulsatile flow. He found that increased intrarenal arterial pressure greatly enhanced natriuresis and that low intrarenal arterial pressure depressed natriuresis. These changes in perfusion pressure did not result in significant changes in GFR. Further, changes in pulse pressure were without effect. These results indicate that the narrowed pulse pressure found distal to a renal artery lesion does not play a role in the functional changes observed in such a kidney and that the filtered sodium load is not the only determinant of sodium excretion in these patients. Rather, decreases in intrarenal arterial pressure may account, in part, for the enhanced sodium reabsorption characteristic of occlusive arterial lesions. As concerns this possibility, mention should be made that at operation in patient no. 28, aortic pressure was 210/120 and renal artery pressure distal to the lesion was 164/120; this is the smallest gradient between aortic and renal artery pressure levels that we have observed in patients with occlusive renal artery disease.

Clinical Significance of Separated Renal Function Tests

Connor, Thomas, Haddock, and Howard[11] have greatly extended the observations of Connor, Thomas, Berthrong, and Howard[2] and again conclude that in patients with hypertension, the finding that one kidney excretes urine of lower volume and sodium content indicates that the kidney is responsible for the hypertension. Our data show that this is commonly, but not necessarily, the case. The renal functional patterns observed in patients with renal hypertension are not dependent upon the vasopressor factor responsible for the raised arterial pressure, but are determined by the location of the lesion which, in some way, causes hypertension, probably through renin release. Accordingly, results of function tests in some patients with bilateral main renal artery lesions may be the same as those of patients with unilateral lesions and also the functional effects of partial or total occlusion of major branches of the main renal artery resemble those of pyelonephritis. Neither branch nor bilateral lesions are uncommon, and in such patients function tests are neither diagnostic nor prognostic. They do provide useful information on relative functional status, but anatomic diagnosis depends on renal angiography.

Summary

Function tests of the individual kidneys have been performed during mannitol diuresis and vasopressin infusion in hypertensive patients with essential hypertension, pyelonephritis, and occlusive lesions of one or both main renal arteries or their primary branches.

In patients with essential hypertension, glomerular filtration rate and renal plasma flow on the two sides, though depressed, were practically equal, as were urine flow, water, solute, and sodium excretions.

Pyelonephritis and branch arterial lesions alike depressed urine flow, glomerular filtration rate, and renal plasma flow in the affected or more-affected kidneys; water, total solute, and sodium excretions were in proportion to glomerular filtration rate. These findings indicate a decrease in numbers of functioning nephrons without a qualitative change in function of those remaining.

Occlusive lesion of one main renal artery decreased glomerular filtration rate and renal plasma flow on the affected side; urine flow was relatively more depressed than filtration rate, urinary osmolality was higher, and urinary sodium concentration was sharply decreased, as was the excreted fraction of the filtered sodium load.

Bilateral occlusive main arterial lesions sometimes had effects similar to those of unilateral lesions in the sense of greater functional deficits on the more-affected sides. However their functional patterns were not consistent.

The enhanced renal sodium reabsorption observed in patients with unilateral and bilateral main renal artery diseases could not be explained solely by decreases in filtered sodium load; this suggests that decreases in intrarenal arterial pressure also affect sodium excretion.

Changes in renal functions caused by ar-

terial disease depend on the site of the lesion and not on the pressor mechanism it may evoke.

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"I rode over to Teddington," wrote Wesley in his diary, "Dr. Hales sent after dinner to desire our company and showed us several experiments," and then this comment: "How well do philosophy and religion agree in a man of sound understanding."—*Diary of John Wesley*, July, 1753.

Ruptured Mitral Chordae Tendineae

By PHILIP J. OSMUNDSON, M.D., JOHN A. CALLAHAN, M.D., AND JESSE E. EDWARDS, M.D.

AMONG THE LESIONS responsible for insufficiency of the mitral valve is rupture of the chordae tendineae. It is our purpose to describe the significant clinical and pathologic findings in 20 cases of insufficiency of the mitral valve due to rupture of the chordae tendineae. This report is based on those cases in which ruptured mitral chordae tendineae were found at necropsy at the Mayo Clinic during the years 1934 to 1958 inclusive.

The important etiologic factors claimed for rupture of the mitral chordae tendineae are bacterial endocarditis,[1-5] rheumatic valvular disease,[6, 7] and trauma.[8, 9] Cases have been encountered, however, in which conclusive evidence of these conditions has not been demonstrated. In those cases in which evidence for a specific etiologic factor is lacking, so-called spontaneous rupture[10, 11] must be considered. Though myocardial infarction is the prominent cause of mitral insufficiency due to ruptured papillary muscles,[12, 13] it has not been demonstrated to be of importance in rupture of the chordae tendineae.

Etiologic Factors of Ruptured Mitral Chordae Tendineae

Bacterial Endocarditis

Bacterial endocarditis is the major factor in the etiology of ruptured chordae tendineae. In the first case of ruptured mitral chordae tendineae reported in the medical literature (Corvisart 1812),[14] necropsy findings were recognizable in retrospect as due to bacterial endocarditis. The association between bacterial endocarditis and ruptured mitral chordae tendineae was well demonstrated in reports by Clark[15] and by Washbourn[1] late in the nineteenth century. Ruptured chordae tendineae have been identified in cases of healed, sometimes clinically unrecognized, bacterial endocarditis[3] as well as in cases of active bacterial endocarditis.

The present study includes 20 cases of ruptured mitral chordae tendineae. In 10 cases there was a history of bacterial endocarditis, active in six cases and healed in four (table 1).

Known Active Bacterial Endocarditis

The microorganisms cultured from the blood of the six patients in this group were *Streptococcus mitis* in two cases, *Streptococcus faecalis* alone in one case and associated with *Aerobacter aerogenes* in another case, and *Escherichia coli* in one case. The blood cultures were repeatedly negative in the sixth case, although active bacterial endocarditis was demonstrated at necropsy. The report of a representative case (case 4) follows.

A 37-year-old woman entered the hospital in February 1953. She had been treated first for bacterial endocarditis caused by *Str. faecalis* 18 months before this admission when weakness, anorexia, and persistent fever had developed. Three months after the onset she had hemiparesis on the right side. Six months later a mycotic aneurysm was excised from the right forearm, and intermittent fever persisted despite continued treatment with antibiotics. Six days before her hospitalization, diplopia and left frontal headache had developed.

On examination a high-pitched systolic murmur of moderate intensity was heard over the precordium which was maximal near the apex of the heart and transmitted posteriorly and to the left. The fingers were clubbed and the liver and spleen were palpable. *Str. faecalis* was cultured from the patient's blood. Treatment with penicillin combined with dihydrostreptomycin was instituted. Suddenly the patient became comatose on her twenty-fourth day in the hospital and died 48 hours later.

At necropsy the heart was found to be moder-

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Supported in part by research grant no. H-4014 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

Abridgment of thesis submitted by Dr. Osmundson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

ately enlarged and weighed 500 Gm. The left ventricle was dilated and hypertrophied and the left atrium was dilated. Both leaflets of the mitral valve were thickened throughout. Many small vegetations were present on the atrial side of the free edge of both leaflets. There was moderate fusion of the leaflets at the posteromedial commissure. Two chordae tendineae of the anterior leaflet, which were located between the midpoint of the leaflet and the anterolateral commissure, were found to be discontinuous from their origins on the anterolateral papillary muscle (fig. 1). These chordae tendineae were thickened and shortened and were the sites of multiple small vegetations. Nearby, intact chordae tendineae also were thickened and were the sites of vegetations. In the left atrium, 0.5 cm. above the lateral portion of the posterior leaflet, was a 3 by 5 cm. portion that was raised, irregular, and had the gross appearance of a jet lesion and mural vegetation. Histologic examination of the heart confirmed the presence of active bacterial endocarditis.

The ruptured chordae tendineae in this case were only one of many complications associated with the active bacterial endocarditis. The site of rupture was in a region of active infection with vegetation formed on the chordae tendineae and mitral leaflet.

Known Healed Bacterial Endocarditis

Ruptured mitral chordae tendineae were found in four cases in which evidence of healed bacterial endocarditis was present at necropsy and in which bacterial endocarditis had been diagnosed during life. Streptococci were the infecting microorganisms in each case and in each case it was stated that the infection had been cured sometime prior to the patient's death. The following case (case 7) is illustrative.

A 42-year-old man was first admitted to the hospital in January 1947 with a history of anorexia, fatigue, and night sweats of 4 months' duration. One month prior to his admission a heart murmur was discovered for the first time. Examination disclosed fever, clubbing of the fingers, and generalized petechiae of the skin. A systolic thrill was noted at the apex of the heart. A loud, rough systolic murmur was heard at the apex and transmitted widely, particularly to the left axilla. A softer systolic murmur was heard at the base of the heart. Cultures of the patient's blood yielded *Streptococcus mitis*. The day after admission, hemiparesis on the left and complete left homonymous hemianopsia developed. Treatment with penicillin was begun and the response was satisfactory.

Examination of the patient in October 1947, 10 months after the initial hospitalization, did not show evidence of active bacterial endocarditis. The patient's cardiac reserve was considered to be good. A loud systolic murmur and an early diastolic murmur were heard.

Later, in September 1950, when the patient was again hospitalized, he gave a history of progressive cough, dyspnea, and dependent edema of 5 months' duration. Atrial fibrillation was present. An apical thrill was noted as well as a harsh apical systolic murmur that was transmitted to the left axilla and posterior part of the thorax on the same side. The diastolic murmur was heard again. A systolic murmur was heard at the base of the heart also. Findings typical of congestive heart failure were present. The patient's condition deteriorated despite treatment and he died on the eleventh day of hospitalization.

At necropsy the heart was found to be enlarged and weighed 600 Gm. The left atrium and the left ventricle were particularly dilated. Both ventricles were hypertrophied. The anterior leaflet of the mitral valve was distorted in the portion adjacent to the posteromedial commissure. Approximately a fourth of the leaflet in this region was devoid of intact chordae tendineae (fig. 2). The leaflet was moderately thickened and arched up into the left atrial cavity. It appeared that there had been a loss of substance of this part of the leaflet. Several of the intact chordae tendineae nearby were slightly thickened. A thickened mural plaque measuring 1.6 cm. in diameter was found on the ventricular wall under the posterior mitral leaflet. This had the appearance of healed mural endocarditis. A jet lesion was found in the left atrium above and posterior to the posteromedial commissure. The other heart valves did not appear to be abnormal.

Histologically, one of the ruptured chordae tendineae had an enlarged fragmented end with calcified and necrotic debris adjacent to the tip. The thickened anterior mitral leaflet was composed of fibrous and collagenous tissue. The plaquelike structure on the endocardium of the left ventricular wall was composed of thickened endocardium with foci of calcified debris. The adjacent fibrous tissue was vascularized.

Mitral insufficiency occurred as a complication of bacterial endocarditis in this case and caused cardiac decompensation that resulted in death. Mitral insufficiency resulted from rupture of the mitral chordae tendineae attached to a portion of the anterior mitral leaflet. Erosion of a portion of the mitral leaflet was an additional complication of the bacterial endocarditis.

Table 1

Summary of Twenty Cases of Ruptured Mitral Chordae Tendineae

Case	Sex; age at death, yr.	Status of bacterial endocarditis at necropsy	Bacterial endocarditis: Infecting micro-organisms	Bacterial endocarditis: Primary site	Healed rheumatic endocarditis	Contribution of ruptured chordae to cardiac disability	Cause of death: cardiac (C) or noncardiac (N)	Number and location of ruptured chordae	Location of jet lesions in left atrium	Transmission of apical systolic murmur	Other abnormalities of mitral valve
1	F 15	Active	Str. mitis	Mitral valve	Present	Contrib.	C	2 Ant. leaflet	Postero-lateral wall	Left axilla; basal precordium	Vegetation, ant. leaflet; chordae fused and shortened
2	M 62	Active	Str. faecalis and A. aerogenes	Mitral valve	—	Contrib.	C	2 Post. leaflet	Anterior septal wall	Left axilla	Vegetation, both leaflets
3	F 69	Active	E. coli	Mitral valve	—	Contrib.	C	8 Ant. leaflet	Postero-lateral wall	Not recorded	Small vegetations, ant. leaflet; fusion of chordae
4	F 37	Active	Str. faecalis	Mitral valve	Probable	Contrib.	N Cerebral embolus	2 Ant. leaflet	Lateral wall	Post. left chest	Shortened post. leaflet; shortened chordae; vegetations, both leaflets
5	M 62	Active	Negative blood cultures	Mitral valve	—	Contrib.	N Cerebral embolus	3 Both leaflets	Anterior wall	Not recorded	Vegetation and distortion of post. leaflet
6	M 64	Active	Str. mitis	Aortic valve	Probable	Contrib.	C	4 Ant. leaflet	Posterior wall	Left axilla	2 Aneurysms of ant. leaflet; small vegetations, ant. leaflet
7	M 46	Healed	Str. mitis	Mitral valve	—	Primary	C	¼ of ant. leaflet without intact chordae	Posterior wall	Left axilla and post. left chest; basal precordium	Ulceration and erosion of ant. leaflet
8	M 65	Healed	Str. (anaerobic) by history	Mitral valve	Present	Contrib.	C	3 Ant. leaflet	None identified	Left axilla	Healed vegetation with distortion of ant. leaflet; thickened chordae
9	M 26	Healed	Str. (type unknown) by history	Aortic valve	Present	Contrib.	N Cerebral embolus	3 Ant. leaflet	Postero-lateral wall	Left axilla; post. left chest	Distortion of ant. leaflet; arching into left atrium
10	M 77	Healed	Str. faecalis	Mitral valve	Present	Noncontrib.	N Atherosclerotic occlusion of basilar artery	1 Post. leaflet	Septal wall, ant. leaflet	Left axilla; basal precordium	Post. leaflet shortened and distorted; fusion and shortening of chordae

11	F 73	Healed	—*	Mitral valve	—	Contrib.	N Carcinoma of colon	1.5 cm. of tissue at anterolateral commissure without intact chordae	None identified	Not recorded	Arching of commissural tissue into left atrium
12	F 80	Healed	—*	Mitral valve	Present	Contrib.	C Broncho-pneumonia	½ of post. leaflet without intact chordae	Septal wall	Basal precordium	Large calcified vegetation, post. leaflet
13	M 49	Healed	—*	Mitral valve	—	Contrib.	C	6 Post. leaflet	Septal wall	Post. left chest; basal precordium	Erosion of post. leaflet
14	F 49	Probable bacterial endocarditis, healed	—*	—	—	Contrib.	N (Undetermined)	5 Ant. leaflet	None identified	Left axilla	Shortening of chordae at anterolateral commissure
15	M 53	Probable bacterial endocarditis, healed	—*	—	—	Primary	N Ruptured cerebral aneurysm	1/3 of post. leaflet without intact chordae	Septal wall	Left axilla; basal precordium	Arching of lateral half of post. leaflet into left atrium
16	M 24	Probable bacterial endocarditis, healed	—*	—	—	Primary	C Cardiac operation	7 Post. leaflet	Septal wall	Left axilla and post. left chest; basal precordium and neck	Arching of post. leaflet into left atrium
17	M 78	Questionable	—*	—	—	Non-contrib.	N Broncho-pneumonia	2 Post. leaflet	Atrial surface of ant. leaflet	Not recorded	Minimal thickening of both leaflets
18	F 87	Questionable	—*	—	—	Non-contrib.	C Pulmonary embolus	2 Post. leaflet	Posterior wall and posterior leaflet	Not recorded	Arching of ¼ of ant. leaflet into left atrium
19	M 52	Questionable	—*	—	—	Primary	C Pulmonary embolus	All to post. leaflet except 3	Septal wall	Post. left chest; basal precordium and neck	Arching of post. leaflet into left atrium
20	F 76	Questionable	—*	—	Questionable	Primary	C	5 to tissue of postero-medial commissure	None identified	Left axilla and post. left chest	Thickened leaflets; shortened post. leaflet; shortened chordae

*No history of bacterial endocarditis.

No History of Bacterial Endocarditis

Pathologic Evidence of Healed Bacterial Endocarditis. Ten of the 20 patients in this study did not have a history of bacterial endocarditis. Necropsy disclosed evidence considered positive for healed bacterial endocarditis in three of the 10 cases, while in an additional three cases the cardiac abnormalities, in addition to the ruptured chordae tendineae, were suggestive though not conclusive evidence of healed bacterial endocarditis. The report of a representative case (case 13) follows.

A 49-year-old man entered the hospital in May 1957. He did not have a history of rheumatic fever or any significant febrile illness. The presence of a heart murmur had been known only since the onset of the patient's symptoms 8 months before his last admission. Exertional dyspnea and dependent edema developed 8 months prior to his admission to the hospital. Orthopnea and paroxysmal nocturnal dyspnea appeared 10 days before his admission.

Physical examination showed the heart to be enlarged. A slight apical thrill was detected. A loud systolic murmur was present over the entire precordium. This was loudest in the fourth intercostal space near the midclavicular line and was transmitted posteriorly and to the left. Rales were present in the lungs; the liver was enlarged to 4 cm. below the right costal margin, and considerable pretibial edema was present. A roentgenogram of the thorax disclosed cardiac enlargement with pulmonary vascular congestion. An electrocardiogram showed a sinus rhythm with multiple premature contractions and nodal escape beats. A subsequent electrocardiogram made 2 days later showed variation between a sinus rhythm and an idioventricular rhythm. The patient did not respond despite intensive treatment for congestive heart failure and died on the fourth hospital day.

At necropsy the heart was found to be moderately enlarged and weighed 430 Gm. All chambers were dilated and the left ventricle particularly was hypertrophied. The mitral valve was the site of considerable abnormality. The posterior mitral leaflet was lacking in substance along its free edge, apparently from an old ulcerative process. The posterior leaflet projected up into the left atrial cavity. Approximately two thirds of the posterior mitral leaflet was without intact chordae tendineae. Remnants of the ruptured chordae were folded under the deformed posterior leaflet and their ends were round and smooth. The anterior mitral leaflet near the anterolateral commissure also appeared to be altered by an ulcerative process, which later healed. A small projection from the posteromedial papillary muscle represented the origin of the ruptured chordae tendineae. The intact chordae tendineae appeared normal. A jet lesion measuring approximately 2 by 3 cm. was present on the septal wall of the left atrium beginning 1 cm. above the anterior mitral leaflet. Histologically the thickened, deformed posterior mitral leaflet was composed of irregular masses of collagenous and fibrous tissue.

This case demonstrates the finding of ruptured chordae tendineae in a patient who did not have a history of bacterial endocarditis but at necropsy definite evidence of healed bacterial endocarditis was found. Mitral insufficiency resulted from rupture of the chordae tendineae and led to the death of the patient.

Without Pathologic Evidence of Healed Bacterial Endocarditis. The cause of ruptured chordae tendineae in the other four cases was not determined. At necropsy evidence of an inflammatory process which had healed prior to the death of the patient was present in each of the four cases, but the lesions were nonspecific and did not allow a precise identification of their causes. The following case is an example (case 16*).

A 23-year-old man was examined in November 1955 for evaluation of a heart murmur first discovered 7 years previously. There was no history of rheumatic fever or trauma to the thorax. Examination of the heart in 1944 gave essentially negative results. In December 1948 an illness began that lasted 6 weeks and was characterized by fever, lassitude, and weakness. The patient was hospitalized during this illness and the roentgenogram of the thorax disclosed inflammation in one lung. The heart murmur was heard first at this time. Exertional dyspnea, severe enough to prevent participation in vigorous activities, was present from the time of this illness. Gradual diminution in the patient's tolerance for exercise developed during the next 5 years.

On first examination at the Mayo Clinic in October 1954, loud systolic murmurs accompanied by thrills were heard over both the aortic and apical areas. Little symptomatic change took place after this visit until 1 month prior to registration in November 1955. At this time the patient experienced dyspnea with minimal exertion, paroxysmal nocturnal dyspnea, vague epigastric discomfort,

*This case formed the basis of a previous publication.[16]

Figure 1

Ruptured chordae tendineae with remnants of ruptured chordae attached to anterior mitral leaflet. Active endocarditis was caused by Streptococcus faecalis. The chordae, involved by vegetations and rupture, are in proximity to areas of infectious activity on the leaflet of the valve (case 4).

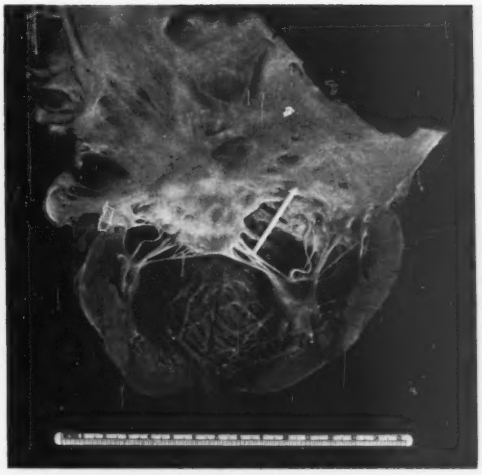

Figure 2

Healed endocarditis due to Streptococcus mitis with ruptured chordae tendineae of the anterior mitral leaflet and erosion of leaflet. The arrow indicates the path of the regurgitant flow and points toward a jet lesion on the posterior portion of the left atrial wall (case 7).

and hemoptysis. Atrial fibrillation was present with an apical rate of 92. A coarse systolic murmur of moderate intensity was present at the second and third intercostal spaces to the right of the sternum and was accompanied by a thrill. This murmur was heard in the neck over the carotid arteries. The second sound in the aortic area was diminished and the second sound in the pulmonic area was accentuated. A loud prolonged systolic murmur of coarse quality, also accompanied by a thrill, was heard at the apex, and was transmitted posteriorly and to the left. A faint early apical diastolic murmur was present. The liver was palpably enlarged.

A roentgenogram of the thorax showed great cardiac enlargement with particular increase in size of the left atrium. The electrocardiograms in 1954 and 1955 were similar and showed changes consistent with left ventricular hypertrophy. The tracings in 1955 also showed atrial fibrillation and ventricular premature contractions.

On the basis of the physical examination and clinical tests, the patient was considered to have aortic stenosis and mitral insufficiency. Catheterization of the right and left sides of the heart was performed. The findings demonstrated mitral insufficiency without aortic stenosis.

An attempt at surgical amelioration of mitral insufficiency was undertaken. At the time of operation the heart was found to be tremendously enlarged, with a huge left atrium. Severe regurgitation of blood through the mitral valve was detectable at the time of digital exploration of the left atrium. An attempt was made to place a circumferential suture around the mitral valve ring in order to reduce the size of the orifice, but this was unsuccessful because of the tremendous dilatation of the mitral ring. The mitral insufficiency was not relieved and the patient died 3 days later.

At necropsy the heart was tremendously enlarged and weighed 1,000 Gm. All chambers were dilated, particularly the left atrium and the left ventricle. Approximately a third of the posterior leaflet lateral to its midpoint was devoid of intact chordae tendineae (fig. 3). The involved part of the leaflet arched into the left atrium giving it a hooded appearance. Seven chordae tendineae arising from the posterior leaflet were discontinuous from their origins at the posteromedial papillary muscle where only one rounded stump remained. The free ends of the chordae appeared irregular and blunt and were hanging free in the ventricular cavity. The leaflets of the mitral valve were intact and slightly thickened in their entirety. The posterior leaflet showed greater thickness near its base. The other valves were normal. A jet lesion was present in the septal wall of the left atrium involving that portion closely approximated to the aortic valve.

Histologically the free ends of the ruptured chordae tendineae had irregular roughened surfaces covered by intact endocardium. The thickening in the posterior mitral leaflet was composed of fibrous tissue that was abundantly vascularized along the atrial surface.

The cause of the ruptured mitral chordae tendineae in this case was not definitely

known. The evidence, although not absolutely conclusive, suggested that bacterial endocarditis had been present. The lesion causing thickening of the base of the posterior mitral leaflet was consistent with a healed vegetation of bacterial endocarditis. The history of the onset of the murmur during a febrile illness further supported the opinion that the ruptured chordae tendineae were a complication of bacterial endocarditis that healed later.

The report of another representative case (case 19) follows.

A 52-year-old farmer was admitted to a hospital in November 1948 because of dyspnea and weakness of 1 year's duration. There was no history of rheumatic fever. The illness leading to hospitalization had begun suddenly in November 1947 when the patient became short of breath after working strenuously to harvest grain. He was unable to work after the onset of this illness and subsequently orthopnea and pedal edema developed accompanied by loss of weight.

Physical examination at the time of admission to the clinic disclosed a blood pressure of 105 mm. Hg systolic and 85 mm. Hg diastolic. A loud harsh apical systolic murmur and a presystolic murmur were heard. A systolic murmur also was heard at the base of the heart with transmission to the vessels in the neck. Venous distention indicated an elevated venous pressure. Pulmonary rales, hepatomegaly, and pedal edema were present. A roentgenogram of the thorax disclosed cardiac enlargement and pulmonary edema.

The patient responded to the prescribed medical program at first, but cough, fever, and hemoptysis developed on the fifteenth hospital day. His condition deteriorated and he died on the twenty-second hospital day.

At necropsy the heart was found to be enlarged and weighed 555 Gm. The left atrium was dilated. Both ventricles were dilated and hypertrophied. The posterior mitral leaflet projected up into the left atrial cavity giving it a hooded appearance (fig. 4). Approximately four fifths of the posterior leaflet was without intact chordae tendineae. Only three chordae tendineae remained intact, and these were in the region near the posteromedial commissure. The other cardiac valves appeared normal. Portions of both the anterolateral and the posteromedial papillary muscles were atrophied. Minimal thickening of the posterior mitral leaflet was present. Neither the remnants of the ruptured chordae tendineae nor the remaining intact chordae tendineae appeared thickened or fused, or the site of vegetation. The endocardium of the septal wall of the left atrium above the anterior mitral leaflet was irregularly roughened and thickened, having the appearance of a jet lesion. A thrombus was present in the right atrial appendage.

Microscopically the ends of the ruptured chordae tendineae were covered by intact endothelium. Moderate fibrosis was present between the muscle fibers and the adjacent papillary muscle. The junction of the papillary muscle with one of the ruptured chordae tendineae was vascularized in one area near the endocardial surface. The microscopic appearance of the left atrial wall in the region of the septum supported the opinion gained from gross examination that this was a jet lesion.

Evidence of a healed inflammatory process in the heart of this patient was minimal. The lesions remaining as residuals of the inflammatory process that had healed prior to death of the patient were not specific enough to allow an etiologic diagnosis. The sudden appearance of cardiac decompensation 1 year prior to death suggested that the chordae tendineae had ruptured at that time.

Other Etiologic Factors. Rheumatic heart disease was a factor of etiologic importance in the 20 cases comprising this study primarily in predisposing to bacterial endocarditis. In each of the five cases with evidence at necropsy of quiescent rheumatic heart disease there also was conclusive evidence of superimposed bacterial endocarditis, active in one case and healed in four cases. In two additional cases necropsy findings were considered suggestive of inactive rheumatic endocarditis and valvulitis. In both cases, evidence of active bacterial endocarditis was found.

No evidence of direct trauma to the thorax of an unusual nature was found in any of the 20 cases. In all cases the findings indicated that the abnormality of the chordae tendineae was acquired and not congenital.

Pathologic Anatomy in Ruptured Mitral Chordae Tendineae

In this series of 20 cases, chordae tendineae arising from the anterolateral papillary muscle were ruptured in nine cases; chordae arising from the posteromedial muscle were ruptured in eight cases; and chordae arising from both groups were ruptured in three cases.

The site of insertion of the chordae tendineae on the valve leaflet is of importance in

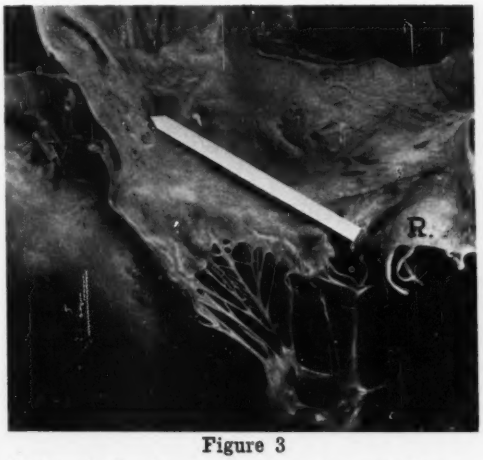

Figure 3

Ruptured chordae tendineae of the posterior mitral leaflet with arching of this portion (R) into the left atrium. An arrow demonstrates the path of the regurgitant blood from the posterior leaflet to the septal wall where a jet lesion is located. The close relationship of the jet lesion and the aortic valve (A.V.) is demonstrated. The septal wall and aortic valve in sagittal section are shown. An artifact is beneath the base of arrow (case 16).

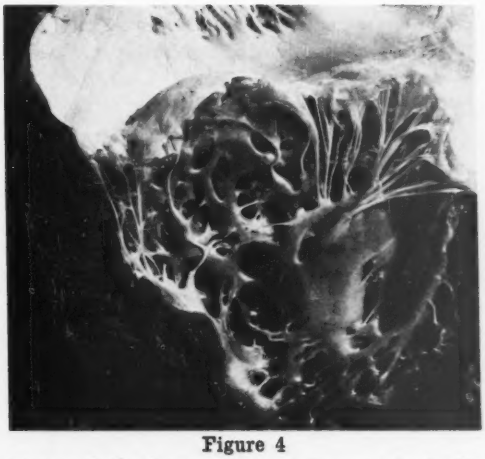

Figure 4

Ruptured chordae tendineae of the posterior leaflet with only remnants of the chordae present on the leaflet. The hooded appearance of the posterior leaflet is demonstrated (case 19).

cases of ruptured chordae tendineae. In the present study, chordae inserting on the anterior leaflet were ruptured in nine cases, those inserting on the posterior leaflet in eight cases, those inserting on both leaflets in one case, those inserting in the region of the anterolateral commissure in one case, and those inserting in the region of the posteromedial commissure in one case.

Ruptured chordae numbered from two to nearly all those inserting on one leaflet. There was a general correlation between the number of ruptured chordae and the degree of mitral insufficiency as estimated at the time of necropsy.

Location of Ruptured Chordae Tendineae

In patients with bacterial endocarditis two important factors apparently influence the location of the ruptured chordae. In cases in which the infection involves the mitral valve it appears that the involved chordae are located adjacent to sites of most active infection. This situation prevailed in 11 of 13 cases in the present series that were considered to have definite evidence of bacterial endocarditis, active or healed, during the patient's life or at necropsy. The mechanism that determined this location appeared to be extension of the infectious process from the leaflet to the adjacent chordae, as stated by Saphir,[4] and by Libman and Friedberg[5] (fig. 1).

The other important factor determining location of the ruptured chordae prevails in a special situation in which bacterial endocarditis involves the aortic valve causing aortic insufficiency. In such a case the regurgitant stream of blood often strikes the ventricular surface of the anterior mitral leaflet and the chordae attaching to the midportion of the anterior mitral leaflet. It is probable that the infectious process extends from the aortic valve to the chordae of the anterior mitral leaflet by this means, with subsequent rupture of the involved chordae. Two cases in this group of 20 demonstrated this situation. In both cases there were residual defects of the aortic cusps resulting from bacterial endocarditis (fig. 5).

Jet Lesions

Endocardial roughening and thickening characteristic of so-called jet lesions were found on the left atrial wall in 16 of the 20 cases. These lesions usually were found on the atrial wall opposite the part of the leaflet

that was the site of the ruptured chordae. Other factors that contributed to the location of the jet lesions were abnormalities of the leaflets such as vegetations, fixed deformities resulting from old vegetations, and loss of valvular substance from ulcerative processes. The jet lesions usually were situated in the lower part of the left atrium (fig. 6).

The manner in which blood regurgitates through the mitral valve in cases of ruptured chordae tendineae can be deduced from certain anatomic findings. In cases in which the ruptured chordae had been present for some time, the involved mitral leaflet could be observed at necropsy to be arched up into the left atrial cavity leaving the leaflet fixed in a characteristic hooded appearance (fig. 4). In cases in which rupture of the chordae probably occurred shortly before death, this finding was not observed. It is postulated that during systole the ruptured chordae allow the involved mitral leaflet to extend beyond its normal position of coaptation with the opposite leaflet and beyond the level of the uninvolved part of the same leaflet. The regurgitant blood striking the leaflet is deflected rather sharply across the left atrium where it strikes the atrial wall or atrial surface of the intact mitral leaflet.

In two of the four cases in which no jet lesions could be definitely identified, some chordae had ruptured that were normally attached in the vicinity of the commissures. It has been postulated that the reason for the infrequent occurrences of left atrial jet lesions in association with rheumatic mitral insufficiency is that the energy of the regurgitant stream is dissipated by the direction the regurgitant stream takes into the left atrium. This also may explain the absence of left atrial jet lesions in these two cases of ruptured chordae to the commissural regions in which, probably, the regurgitant stream was directed more centrally into the left atrial cavity.

Findings in Study of Clinical Records

Murmurs

The theory has been advanced that the location of jet lesions may explain some of the characteristics of heart murmurs.[17, 18] The location of the ruptured chordae (the particular portion of the leaflet that allows regurgitation) and the evidence of jet lesions in the left atrium form the anatomic bases for an explanation of some characteristics of the murmurs.

The murmur most frequently recorded in this series of cases was an apical systolic murmur, which was present in every case. The adjectives used to describe the murmurs varied considerably but included the terms "harsh," "high pitched," "whistling," "blowing," and "coarse," as well as various estimations of the intensity. An associated systolic thrill at the apex was recorded in five cases. In the cases in which no lesions of other valves existed, a diastolic murmur was recorded in three instances. This was specifically described in one patient as a presystolic component of the systolic murmur.

In the group as a whole there was no uniformity in the transmission of the systolic murmurs. The areas to which transmission occurred were those in which the murmur of mitral insufficiency is typically transmitted, namely, the left axilla, the left posterior portion of the thorax, and the basal area of the precordium. There appeared to be a definite correlation between the location of the ruptured chordae and the transmission of murmurs in some cases.

Definite left atrial jet lesions were recognized in all eight cases involving chordae of the posterior leaflet. In one case the jet lesion was located on the anterior mitral leaflet opposite the site of ruptured chordae. In seven cases the lesions were located on the septal wall of the left atrium. In one case of rupture of chordae to the posterior mitral leaflet the jet lesion was located in the septal wall of the left atrium adjacent to the aortic valve (fig. 3). The apical systolic murmur was transmitted to the aortic area and to the vessels of the neck; it simulated the murmur of aortic stenosis. The proximity of the jet lesion to the aortic valve forms the anatomic basis for the theory of the production of the aortic systolic murmur in this case.

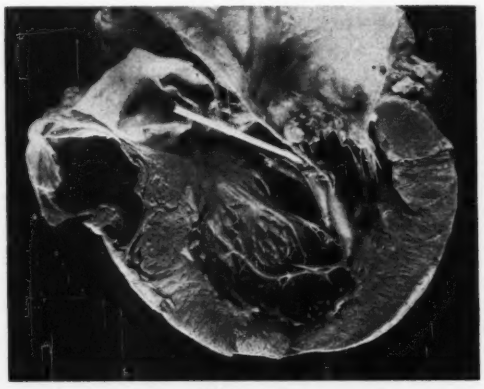

Figure 5

Case 6. Active endocarditis due to Streptococcus mitis with involvement of the aortic valve, with aortic insufficiency and secondary spread of the infectious process to the chordae of the anterior mitral leaflet. Vegetations on the chordae are demonstrated. Ruptured chordae, though not clearly evident, were located in the region of this infectious activity. (The arrow points in the presumed direction of the regurgitant stream originating at the aortic valve.)

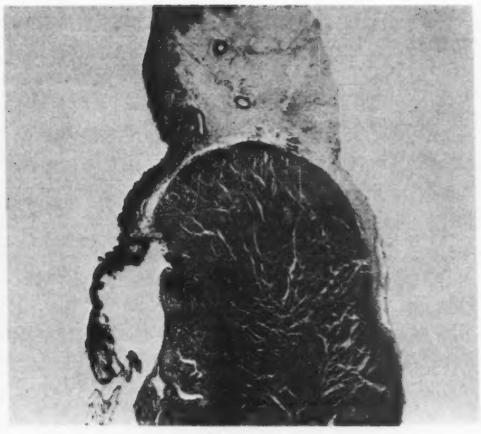

Figure 6

Case 6. Section of left ventricle, left atrium, and posterior mitral leaflet in case of ruptured chordae tendineae of the anterior mitral leaflet shown in figure 5. The jet lesion on the left atrial wall and adjacent posterior mitral leaflet is demonstrated. Verhoeff's elastic-tissue stain counterstained with van Gieson's connective tissue stain.

An additional patient in the present study (case 19) had auscultatory findings similar to those in the case described (case 16). These findings were a basal systolic murmur with transmission to the cervical vessels in addition to the apical systolic murmur. The aortic valve was normal at necropsy in this case also, and the jet lesions on the septal wall were anatomically close to the aortic valve.

Two other cases of mitral insufficiency due to ruptured chordae tendineae simulating aortic stenosis have been described.[19, 20] In both cases, however, the chordae to the anterior mitral leaflet were ruptured rather than the chordae to the posterior mitral leaflet. In one the jet lesions were partially adjacent to the aortic valve, but in the other the jet lesions were on the posterior atrial wall.

In the present study there were four other cases in which ruptured chordae of the posterior leaflet were found and basal systolic murmurs were recorded. Thus, in six of the eight cases with ruptured chordae of the posterior leaflet, transmission of an apical systolic murmur to the basal area of the precordium was present. In these eight cases the apical systolic murmur was transmitted also to the left axilla in three, to the posterior left part of the thorax in two, and to both of these areas in one case. An anatomic basis for the transmission of the murmurs posteriorly to the left in these cases was not apparent.

Jet lesions were identified in the left atrium in seven of the nine cases in which the anterior leaflet was the site of the ruptured chordae tendineae. The location in the atrial wall ranged from the posteromedial atrial wall to the lateral wall, being generally opposite the site of incompetency of the anterior leaflet.

The systolic murmurs were heard in other areas in addition to the apex in seven of the nine cases. The apical systolic murmur was transmitted to the left axilla and posterior portion of the left side of the thorax in two, to the left axilla alone in four, and to the posterior left portion of the thorax alone in one. Basal systolic murmurs were recorded in four cases in this subgroup of nine cases, but in two cases aortic stenosis was verified at necropsy, while in two cases the aortic valve was not stenotic.

The findings relating particularly to the transmission of the apical systolic murmur to the basal precordial areas in cases with rupture of chordae to the posterior leaflet, and those relating to the transmission of the murmurs posteriorly to the left in cases with rupture of chordae to the anterior leaflet, offer support to the theory that the transmission of murmurs is related in part to the direction of regurgitant flow and possibly to the impact of blood on the left atrial wall. The lack of complete correlation between the sites of rupture and the location of the jet lesions to the areas in which the murmurs were recorded in these cases suggests that there are other factors that were not apparent.

Time of Rupture of Chordae Tendineae

The sudden appearance of a previously unrecognized precordial systolic murmur has been considered to be of significance in the diagnosis of ruptured mitral chordae tendineae.[7] This situation, however, was not sufficiently well defined in any case in the present study to provide evidence for ruptured chordae as the cause of the mitral insufficiency. It was impossible to determine the time of appearance of the murmurs except in three instances in which a murmur was known to have begun during active bacterial endocarditis.

In those cases in which heart murmurs were known to be present prior to bacterial endocarditis, there was no good evidence for definite or significant change of the murmurs during the bacterial endocarditis.

Cardiac Decompensation

The sudden onset of cardiac decompensation or a sudden worsening of the state of cardiac compensation has been noted previously in patients with rupture of the mitral chordae tendineae.[10, 11] It has been postulated that this event may be temporally related to the rupture. This phenomenon was present in two cases in the present study (cases 19 and 20).

In these two cases the rapid and sudden appearance of symptoms and signs of cardiac decompensation appeared 12 and 11 months prior to death, respectively. In one of them (case 19) an apical systolic heart murmur was noted prior to this sudden appearance of failure. The characteristics of the murmurs were not significantly changed during the course of this patient's illness.

The clinical features of these two cases bear certain resemblances to those of the cases of spontaneous rupture of the mitral chordae tendineae reported by Horton-Smith,[10] Frothingham and Hass,[11] and one of the cases reported by Bailey and Hickam.[7]

Signs and symptoms of cardiac decompensation were present in 16 of 20 cases in this study. In four cases cardiac decompensation was minimal, and in each of these only one or two ruptured chordae were found. In the patients in whom ruptured chordae were the primary factors in the cardiac disability there was a good correlation between the severity of the heart disease and the number of ruptured chordae.

Discussion

Bacterial endocarditis was the factor of major etiologic importance in the cases in this study. Of the 20 cases presented, bacterial endocarditis was known to be present during life in 10. In these cases necropsy showed the infection to be active in six and healed in four. In the other 10 cases there was no history of bacterial endocarditis, but in three of these there were findings at necropsy that were interpreted as those of healed bacterial endocarditis. In three additional cases necropsy findings were less definite but nevertheless suggestive of healed bacterial endocarditis. In the remaining four cases residual abnormalities from inflammatory processes in the heart were demonstrated but these changes were not specific. Mitral insufficiency in patients who have had bacterial endocarditis may be the result of one or of several abnormalities in addition to rupture of the chordae tendineae. These include destruction of the leaflet tissue, fixation of the posterior leaflet to the left ventricular wall by organized vegetations, and distortion of the leaflets by large vegetations and enlargement of the mitral orifice.[17] In the 20 cases of this study, rupture of the chordae tendineae was the primary factor in mitral insufficiency in five.

The role of rheumatic endocarditis in the production of rupture of mitral chordae tendineae is not completely known. In some cases, rheumatic endocarditis predisposes to bacterial endocarditis even to the location of bacterial vegetations on the valve-chordae complex. Cases were encountered in the present series in which the inflammatory changes observed were suggestive of healed rheumatic endocarditis, and convincing evidence, either clinical or pathologic, could not be found for superimposed bacterial endocarditis. It is perhaps possible also that chordae tendineae, involved by rheumatic endocarditis, could rupture spontaneously.

In the present series, the microorganisms responsible for bacterial endocarditis were largely streptococci of different varieties. The antibacterial measures now available effect a cure in a great many cases owing to streptococci.[21] In such cases little evidence might remain at necropsy of previous bacterial endocarditis. It seems possible that bacterial endocarditis, whether clinically recognized or not, could be responsible for rupture of mitral chordae tendineae and still not show pathognomonic evidence of its existence.

Two cases in the present study (cases 19 and 20) and three reported previously,[7, 10, 11] suggest that rupture of chordae tendineae did not occur during active inflammation. The two patients in this series apparently were in good health when dyspnea developed rather suddenly after a period of unusually heavy exertion. Dyspnea initiated serious cardiac decompensation and these two patients died 11 and 12 months later, respectively. It is postulated that the rupture of the chordae tendineae occurred near the time of onset of dyspnea.

Rupture of mitral chordae tendineae might be responsible for the production of new murmurs. In the cases in this study, recognition of the beginning of cardiac murmurs was not a useful clinical event. The principal difficulty in making the diagnosis of ruptured mitral chordae tendineae on a clinical basis would seem to be in differentiating it from other causes of mitral insufficiency. Ruptured mitral chordae tendineae as a cause of mitral insufficiency might be suspected, but probably a definite diagnosis would be difficult or impossible clinically. The appearance of mitral insufficiency in association with bacterial endocarditis or with a febrile illness which was not definitely identified, or in which the transmission of the murmur seemed to be in keeping with the anatomic varieties discussed previously, should be considered suggestive. Recent surgical advances in the treatment of mitral insufficiency have led to increased interest in the entire problem. A technic for surgical correction of mitral insufficiency due to ruptured mitral chordae has been described by McGoon.[22] Fortunately it is not vital to make this difficult specific diagnosis before exposing the mitral valve at the time of open-heart operation.

Summary

The present study presents pertinent clinical and pathologic findings in 20 cases of ruptured mitral chordae tendineae encountered at the Mayo Clinic between 1934 and 1958 inclusive. Mitral insufficiency results from the rupture of chordae tendineae, the severity being related to the number of chordae ruptured. The resulting heart disease may be severe and may progress to cardiac decompensation and death. Bacterial endocarditis was the major etiologic factor in rupture of the chordae tendineae in this study.

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The area of the transverse section of the pulmonary artery being in one part, before it divaricates into branches, of the same dimension with the orifice of the *aorta,* the velocity of the blood in that part may be accounted the same as in the orifice of the *aorta.* But though the quantities and velocities of the blood, in passing out of both ventricles, be the same, yet it does not thence follow, that their expulsive forces must be both the same: for if the blood in passing into the pulmonary artery, finds less resistance from the preceding blood, than the blood does in entering into the *aorta,* then a less force will expel it out of the right ventricle with equal velocity; and accordingly, as there is not so much force required to drive the blood thro' the lungs, as thro' the rest of the whole body, so we may observe, that the substance of the muscle of the right ventricle has not near the thickness of that of the left.—STEPHEN HALES, B.D., F.R.S., *Haemastatics,* Vol. II, London, 1733.

Myocardial Blood Flow and Oxygen Consumption during Postprandial Lipemia and Heparin-Induced Lipolysis

By TIMOTHY J. REGAN, M.D., KENAN BINAK, M.D., SEYMOUR GORDON, M.D., VALENTINO DEFAZIO, M.D., AND HARPER K. HELLEMS, M.D.

ALTHOUGH the status of regional vascular tone and total cardiac output have been established as important determinants of regional blood flow, the precise role of the physical state of circulating blood has not been extensively explored. A study by Kety[1] in man has indicated that the increased corpuscular mass of polycythemia vera can be associated with a reduced cerebral blood flow. The induction of plasma lactescence in man after high lipid ingestion may also result in alterations of regional blood flow. Erythrocyte aggregation with circulatory slowing has been observed as a consequence of this postprandial circumstance,[2] and varied clinical data have been accumulated to assign to it a pathogenetic basis for cardiac ischemia.[2, 3] To assess the consequences of the postprandial lipemic state upon myocardial blood flow and oxygen consumption these parameters have been studied during maximal plasma lactescence, and contrasted with the findings during post-heparin clearing and with data obtained in a group of fasting control subjects.

Materials and Methods

Both the 15 control subjects studied after an overnight fast and the group of 14 studied during the postprandial state were selected during the end of the recovery phase of their illness just prior to hospital discharge. All were male and comparable in age distribution. Similar afflictions were present in both groups, usually benign, acute bacterial infections of the lung, skin, or kidney. Patients with probable hemodynamic or pathologic alterations of the cardiovascular system were excluded, as were additional subjects, who did not fulfill hemodynamic criteria for normalcy, in most instances ascribable to anxiety. These requirements included a pulse rate of 60 to 95, a total body oxygen consumption of less than 160 ml. per square meter, a systemic arterial pressure less than 140/90 mm. Hg, a systemic arterial mixed venous oxygen difference between 35 and 45 ml. per liter of blood, and a cardiac index between 2.5 and 4.5 liters per minute per square meter.

The group of 14 were fed 1.5 Gm. of lipid per Kg. in cream (36 per cent fat) about 3 hours before the catheters were placed in the coronary sinus and right atrium and a Cournand needle was inserted into the brachial artery. Lumens were maintained patent by slow saline infusions, the lipid-clearing agents, heparin and glucose, being avoided. Since employment of the Fick principle for blood-flow determinations requires a steady state, serial total oxygen consumptions were performed to assess the postprandial alterations in 5 patients. The peak increment of total oxygen consumption occurred at 2 to 2½ hours, and by 3 hours a level was reached slightly higher than the control value. There was for the group no difference between the 3-hour and 3½-hour oxygen consumptions, 143 ± 11.1 ml. and 142 ± 12 ml. per minute, respectively. At approximately 3 hours and 15 minutes post cibum, the first coronary blood flow was determined by the nitrous oxide desaturation technic,[4] immediately followed by simultaneous sampling for blood oxygen and carbon dioxide from the brachial artery, coronary sinus, and right atrium. Concurrently the expired air was collected for Fick cardiac output determinations, and the brachial artery pressure was recorded.

To induce lactescence-clearing, 60 mg. of heparin were then injected intravenously. After an initial increment during the rapid phase of lipid hydrolysis, serial total oxygen consumption determinations were found to remain relatively steady. Coronary and systemic hemodynamics were restudied 45 minutes after heparin administration. The small difference in total oxygen consumptions, prior to and following this repeat nitrous oxide inhalation,

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Supported by grant H-1492, National Heart Institute, National Institutes of Health, U.S. Public Health Service; Michigan Heart Association; and the Receiving Hospital Research Corporation.

Presented in part at the Annual Meeting of the American Society for Clinical Investigation, Atlantic City, New Jersey, May 4, 1959.

169 ± 11 ml. and 164 ± 9 ml. per minute, respectively, indicated that a relatively steady state had been achieved.

In the group of 14 patients evaluated in this manner, serial arterial samples for plasma turbidity measurement were secured from 2½ hours post cibum, at 15-minute intervals, until the experiment was concluded. These specimens were collected in chilled tubes, refrigerated, and read at 650 and 700 mμ on the Junior Coleman spectrophotometer. These are the usual wavelengths employed for measuring turbidity and are far enough removed from the optimal wavelengths for plasma pigments, such as hemoglobin, to avoid interference. A comparison of the readings at both wavelengths showed the 700 mμ value to be slightly lower, but the relationship of the serial turbidity values at each wavelength was the same. The readings reported are those obtained at 650 mμ.

The development of plasma lactescence during alimentary lipemia has been alleged to be dependent upon triglyceride concentration.[5] Several in vitro studies have noted a lack of correlation between these two entities. More recently, plasma turbidity has been exhibited in man after a lipid meal in the absence of significant alteration of serum triglyceride.[6] For these reasons, the physicochemical change in blood evidenced as lactescence, rather than the concentration of lipids, has been correlated with the coronary hemodynamic data.

A valid use of the nitrous oxide method for analysis of regional blood flow in the circumstances of the study requires that the solubility of this gas in blood be unaltered by the quantity of lipids present in the lipemic state. That the solubility of nitrous oxide may not be affected by lipid is indicated by studies of its solubility in brain, where it was not significantly greater than in blood.[7] The partition coefficient, according to Kety,[8] would be expected to change significantly only with such an altered composition of brain or blood as to be incompatible with life.

During postprandial lipemia, if one assumes lipid concentration to be higher in blood than in heart, a possible increase in nitrous oxide blood solubility would diminish the partition coefficient and thus the low flows recorded should actually be still lower. That the nitrous oxide is not more soluble in the postprandial lipemic blood is indicated by the nitrous oxide value of arterial samples after saturation achieved by 12 minutes' inhalation of this gas. The lactescent samples did not differ significantly from the post-heparin samples. Instead of the higher value to be expected if the gas were more soluble, the mean lactescent figure was 0.2 volumes per cent lower than the post-heparin value.

Although no difference in lactescence was found between arterial and coronary sinus blood (0.01 ± 0.03), the arterial lipid concentration was probably higher than venous, and raises the question of a higher nitrous oxide solubility in arterial blood. This would give falsely high nitrous oxide arterial concentrations and, in the desaturation method, a narrowing of the integrated arteriovenous difference. Thus, the low coronary flow level found would actually be higher than the true value unaffected by a spurious arteriovenous difference. These considerations, based upon a slightly higher concentration of lipid in the arterial blood, are seen to be of no importance, since the arterial samples saturated with nitrous oxide do not differ in concentration despite a nearly 3-fold difference in turbidity and a probable lipid difference amounting to several thousand milligrams. After heparin, a higher lipid concentration in the myocardium probably occurs and might increase the tissue/blood solubility. If the partition coefficient increases, the numerator of the nitrous oxide Fick equation would, unless corrected, be somewhat low. Consequently, the return of coronary blood flow from low to normal levels, as detailed in the results, would be qualitatively correct even if the real change were greater. Despite these considerations, a significant nitrous oxide solubility change appears unlikely.[7, 8]

Results

Considerable variation existed in the actual level of lactescence after a lipid meal. The seven of 14 patients in whom substantial lipemia occurred, with optical density readings above 0.3 unit, were selected for evaluation of the lipemic state and are termed the lipemic group. The individual and mean values obtained from 15 fasting controls are detailed in table 1. The coronary blood flow for this control group (83 ml. per 100 Gm. per minute) was significantly higher than the postprandial flow of 67 ml. in the lipemic group ($p = <0.001$) outlined in table 2. As a consequence of this flow reduction, the consumption of oxygen by the heart was, at 7.02 ml. per 100 Gm. per minute, diminished more than 20 per cent in contrast to the control fasting group value of 9.00 ml. per 100 Gm. per minute ($p = <0.05$). This deficit occurred in the absence of any increment of oxygen extraction, since the myocardial arteriovenous difference of oxygen in the lipemic group (10.54 volumes per cent) is no higher than the 11.02

Table 1

Hemodynamic Data in Fifteen Fasting Normal Subjects

Patient, age, sex	BSA M.²	Coronary blood flow ml./100 Gm./min.	Myocardial: Oxygen arteriovenous difference	Myocardial: Oxygen consumption ml./100 Gm./min.	Cardiac index L./min./M.² BSA	Pulse rate	Mean arterial pressure mm. Hg	Left ventricular stroke work index Gm. M./beat/M.²
R. McS. 31, M.	1.84	84	10.73	9.00	3.26	75	81	47.9
F. E. 40, M.	1.69	80	12.20	9.80	4.20	87	99	64.6
W. C. 29, M.	1.63	99	8.60	8.50	4.01	87	92	57.5
L. M. 45, M.	1.73	70	11.05	7.70	3.21	79	77	54.4
C. A. 41, M.	1.78	83	11.99	10.00	3.22	94	102	47.0
R. W. 35, M.	1.74	73	12.99	9.40	2.76	74	86	43.5
S. A. 32, M.	1.60	70	11.02	7.71	3.09	60	92	63.8
M. F. 40, M.	1.70	96	11.22	10.77	3.09	74	95	54.7
R. F. 38, M.	1.73	92	11.99	11.00	3.52	74	94	60.0
J. L. 56, M.	1.80	76	10.99	8.28	3.46	70	88	59.2
W. A. 30, M.	1.59	84	10.12	8.50	3.54	88	80	40.2
J. A. 29, M.	1.94	98	9.79	9.62	3.55	69	90	61.9
F. C. 30, M.	1.72	77	10.75	7.76	3.26	68	92	59.3
G. T. 37, M.	1.87	74	9.72	7.20	2.75	77	94	44.7
A. K. 43, M.	1.83	87	11.07	9.64	3.33	83	98	54.0
Mean values		83	10.94	9.00	3.35	77	90	54.2

volumes per cent of the control fasting subjects. The relevant hemodynamic indices of pulse, mean arterial pressure, cardiac index, and stroke work index were not significantly different between the two groups. Whole blood viscosity was measured in 2 patients during lipemia* the values of 4.46 and 4.74 centipoise units, obtained on a rotating disk viscometer,† were within the limits found in fasting normal subjects.

During the process of heparin-induced lipolysis, plasma lactescence was reduced from a mean of 0.65 optical-density unit to 0.25 unit, 45 minutes after 60 mg. of intravenous heparin, when the repeat determination of coronary hemodynamics was performed. The initially low coronary flow during lactescence was in each instance restored toward normal during the clearing process from a mean of 67 ml. to 87 ml. per minute per 100 Gm. of left ventricle ($p = < 0.02$) (fig. 1). This change was paralleled by an augmented myocardial oxygen consumption from 7.02 to 9.57 ml. per 100 Gm. per minute ($p = < 0.05$). The

*Through the courtesy of Dr. Perry C. Martineau, Department of Pathology, Wayne State University College of Medicine, Detroit, Mich.

†Brookfield Engineering Laboratory, Stoughton, Mass.

Table 2

Hemodynamic Data in Seven Patients during the Lipemic State and after Heparin-Induced Lipolysis

Patient, age, sex	BSA $M.^2$	Optical-density units	Coronary blood flow ml./100 Gm./min.	Oxygen arteriovenous difference volume %	Myocardial: Oxygen consumption ml./100 Gm./min.	Myocardial: Cardiac index L./min./$M.^2$ BSA	Pulse rate	Mean arterial pressure mm. Hg	Left ventricular stroke work index Gm. M./beat/$M.^2$	Arterial oxygen saturation %
L. H.		.502*	61	10.39	6.34	3.48	73	80	51.9	92.5
24, M.	1.83	.070†	71	9.94	7.06	3.59	74	72	47.5	94.9
V. D.		.740*	72	11.81	8.50	3.35	60	87	66.5	95.4
22, M.	1.82	.323†	83	11.51	9.55	4.21	66	93	79.7	93.0
W. McC.		.790*	74	10.09	7.47	2.54	80	89	40.0	93.8
35, M.	1.83	.340†	80	10.36	8.29	2.94	83	91	45.9	98.7
H. W.		.640*	69	8.96	6.18	3.58	73	103	69.2	92.7
53, M.	1.77	.171†	82	10.89	8.93	3.14	78	110	60.0	97.2
G. B.		.410*	69	11.27	7.78	2.83	84	88	41.0	97.7
58, M.	1.72	.110†	89	10.98	9.77	3.35	91	80	36.0	96.0
W. B.		.550*	57	12.71	7.24	3.01	71	92	53.1	94.8
44, M.	1.70	.140†	108	13.39	14.46	3.42	76	98	60.0	
E. B.		.890*	66	8.55	5.64	2.76	83	102	38.0	96.7
42, M.	1.93	.620†	98	9.11	8.93	2.45	86	104	40.2	98.9
Mean		.646*	67	10.54	7.02	3.08	75	92	51.4	94.8
values		.253†	87	10.88	9.57	3.35	79	93	52.7	96.8
p		<0.001‡	<0.01	>0.10	<0.01	>0.10	<0.01	>0.10	>0.10	
values			<0.02§	>0.10	<0.05	>0.10	>0.05	>0.10	>0.10	>0.10

*Lipemic state.

†Post heparin.

‡Lipemic state compared to fasting controls of table 1.

§Lipemic state compared to values in same patient after heparin.

increment is largely ascribable to flow alteration as the oxygen extraction was relatively unchanged. The over-all response to heparin lipolysis entailed no significant rise in the cardiac index, pulse rate, mean arterial blood pressure, or stroke work index (table 2) that may have accounted for the observed facilitation of myocardial oxygen usage. Since this effect may rather have been achieved by a property of heparin unrelated to lipolysis, its activity in the absence of clearing effect has been analyzed in a group of 6 patients, 3 of whom were fasting. The remainder had low lactescence levels that were not altered by heparin. In this situation, heparin failed to increase the coronary blood flow (fig. 2). Instead, a slight decline in myocardial oxygen consumption was detected.

The relative state of the myocardial respiratory quotients compared to the simultaneous oxygen consumption is illustrated in figure 3. The low levels found in the fasting state are attributable to the dependence upon lipid as the major source of energy supply in this circumstance.[9, 10] In both the fasting normal group and in the postprandial lipemic group with a lower level of oxygen consumption, there was no difference in the comparative respiratory quotient. The unchanged repiratory quotient associated with heparin-induced lipolysis implies that accelerated fatty acid utilization has not yet occurred in this lipid-loading situation.

The data in the 7 patients in whom lactescence readings after lipid feeding were below 0.3 optical-density unit are given in table 3. The coronary blood flow and myocardial oxygen consumption did not differ significantly from the control group. In the 4 who received heparin, neither lactescence nor coronary dynamics underwent substantial change, additional characteristics that mark the difference between the fully developed lipemic state and the abortive form seen in this group.

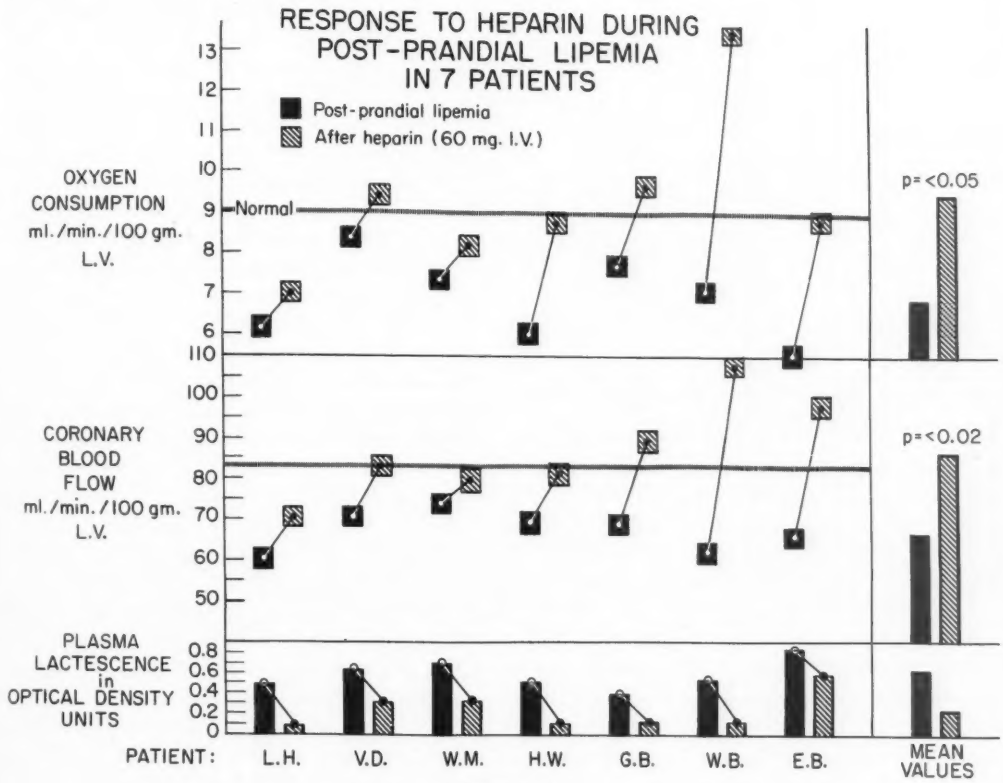

Figure 1

Response to heparin during postprandial lipemia in 7 patients.

Discussion

The data from this study indicate that the development of a sufficient degree of plasma lactescence during the course of alimentary lipemia will limit oxygen delivery to the overtly normal myocardium. Definite evidence bearing on the basis for this concentration-dependent phenomenon in the resting state is lacking. Preliminary information indicates, however, that the enhanced circulatory requirements of the exercised lipemic patient are indeed restricted even at low lactescence values.[11] Failure of the anticipated increments of oxygen extraction to compensate for the reduction of myocardial blood flow may be attributable to the phenomenon of erythrocyte aggregation, observed in the conjunctival vessels of man.[2] A firm causal relationship in the myocardium itself remains to be established.

Since metabolic events within the myocardium may exert a controlling influence upon the rate of coronary blood flow,[12] it is conceivable that the depressed myocardial oxygen consumption during lipemia in the absence of significant hemodynamic alterations is related to a shift in substrate utilized for energy production. Other data indicate that the relative usage of carbohydrate and fat by the heart seems reasonably well reflected in the simultaneous respiratory quotient.[10] The stability of this parameter under the three conditions studied implies that, even if the heart is extracting lipid in response to high extrinsic concentrations, significant utilization has not yet occurred in accord with the storage con-

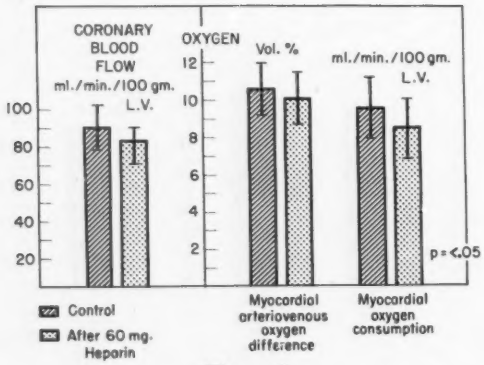

Figure 2

Response of 6 patients to heparin without lipolysis. I represents the standard deviation.

cept derived from lipid loading studies.[9] Despite the lack of gross metabolic change, one cannot exclude a critical effect upon a metabolic locus inaccessible to in vivo methods. Whether myocardial oxygen consumption can be stimulated by rapid presentation of foodstuff to the myocardium is a problem raised by the probability of abrupt increase in lipid extraction during post-heparin lipolysis.[14] Such stimulation does not occur when high lactescence levels are present and the myocardium is presented with large amounts of lipid. Moreover, the absence of changes in cardiac oxygen consumption during intravenous glucose[13] and infusion of amino acid[9] would indicate that a nonspecific foodstuff stimulation of oxygen consumption is unlikely.

Although these studies confirm the capacity of a lipemia-inducing meal to modify the circulatory status of certain organs, the significance of the alteration in oxygen delivery in the presence of an unaltered work load is uncertain. In addition to the fact that no clinical or electrocardiographic consequences were elicited, prior experience with anemic subjects[15] and patients inspiring 10 per cent oxygen for 30 minutes[16] have indicated that this degree of limitation to oxygen delivery may occur without apparent impairment of function in otherwise normal hearts. In 25 per cent of both groups, the myocardial oxygen consumption was less than 7.3 ml. per 100 Gm. per minute.

It is equally difficult to assign a deleterious role to the lipemic state in the heart with coronary artery disease, even with the assumption of a similar effect on oxygen uptake as observed in the normal. For it would then seem necessary to postulate a differential effect upon oxygen delivery with the establishment of an oxygen gradient within the myocardium. Certainly the sparseness of clinical reports to date, intimating an association of lactescence and angina pectoris, suggests that such a relationship may be found in but a minority of patients. Nevertheless, it is conceivable that in the development of coronary thrombosis the lipemic state may have pathogenetic significance related to the induction of circulatory slowing and accelerated coagulation activity[17] within an atherosclerotic vessel.

Employing the usual oxygen energy equivalent,[18] one may consider an enhanced mechanical efficiency of the heart to exist in the lipemic state. An accurate estimation of efficiency is not obtainable, however, without knowledge of the relative status of oxygen usage during the different phases of the cardiac cycle. Conceivably, the oxygen utilized and energy liberated during the part of the cycle concerned with external cardiac work may be unaltered.[18]

Although the usual mechanism for accomplishing a decline in regional blood flow in the absence of systemic hemodynamic changes is through enhanced arteriolar resistance, the observation of abnormal erythrocyte aggregations in human conjunctival vessels during lipemia[2] implies that the modification in flow may be achieved more by an increase in viscosity than in vasomotor tone. While viscosity has been demonstrated to rise in certain animal studies, the alterations associated with circulatory slowing may occur in the absence of a measurable increase in blood viscosity,[19] which conforms to the findings in 2 subjects of the postprandial lipemic group studied by the shear-viscosity method. The methodologic difficulties of in vitro viscosimetry have been emphasized by the disappearance of erythrocyte aggregation in freshly drawn blood.[20]

Even more perplexing is the problem of duplicating the geometry of the components of the vascular system and their varied effects upon cellular deformation.[2, 20] Whatever the actual status of blood viscosity, this factor alone would not account for the observed decrement in cardiac oxygen consumption. A substantial restriction of blood flow to the brain occurs in erythremia associated with enhanced viscosity, yet cerebral oxygen consumption is maintained by virtue of a larger oxygen extraction.[1] Thus, the lack of anticipated increment in oxygen extraction during lipemia suggests an impaired blood-tissue oxygen transport, perhaps related to the abnormal aggregation of red cells observed by others.[2]

The prevalence of this phenomenon of reduced myocardial blood flow and oxygen consumption following the rather unphysiologic circumstance of a predominantly fat meal appears to depend upon an abnormal response to mixed feeding. Even though modest amounts of available carbohydrate appear to minimize the degree of alimentary lipemia in normal subjects,[21] it remains conceivable that the metabolic processes associated with coronary atherosclerosis may involve an aberrant lipid transport mechanism[22] so that substantial lipemia ensues in a nutritional circumstance in which this would be normally improbable.

Summary

The role of the physical state of plasma as a determinant of oxygen availability to the myocardium has been investigated during the course of alimentary lipemia. After the development of substantial plasma lactescence, the coronary blood flow (nitrous oxide method) and myocardial oxygen consumption were assessed in 7 normal human subjects and repeated after heparin-induced lipolysis. The lipemic state was further contrasted with a control fasting group, comparable in age and sex.

The mean coronary blood flow for 15 fasting controls was 83 ml. per 100 Gm. of left ventricle per minute with a myocardial oxygen extraction of 11.04 volumes per cent, and a myocardial oxygen consumption of 9.0 ml. per 100 Gm. of left ventricle per minute. By contrast, the mean coronary blood flow during maximal lipemia in the 7 subjects fed cream was 20 per cent below normal, with a value of 67 ml. per 100 Gm. per minute ($p = < 0.01$). As the extraction of oxygen was not significantly affected, the calculated myocardial oxygen consumption was proportionately reduced to 7.02 ml. per 100 Gm. per minute ($p = < 0.01$). A failure of the anticipated oxygen extraction increment in the face of coronary blood flow reduction suggests an impediment of blood-tissue oxygen transport during lipemia.

After the administration of 60 mg. of heparin to the 7 lipemic subjects, a 65 per cent decline in plasma lactescence was observed by 45 minutes, when the coronary blood flow and myocardial oxygen consumption were elevated to 87 ml. per 100 Gm. per minute ($p = < 0.05$) respectively. Thus, the reduced coronary flow and myocardial oxygen consumption were restored in each instance to normal levels during the process of plasma clearing. There were no associated systemic hemodynamic changes to account for such in-

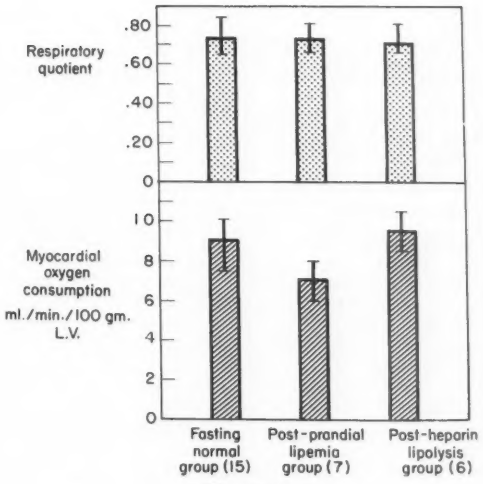

Figure 3

Comparative myocardial respiratory quotients and oxygen consumptions. I *represents the standard deviation.*

Table 3

Hemodynamic Data in Seven Patients with Low Lactescence and in Four after Heparin

Patient, age, sex	BSA M.²	Optical-density units	Coronary blood flow ml./100 Gm./min.	Myocardial: Oxygen arteriovenous difference volume %	Myocardial: Oxygen consumption ml./100 Gm./min.	Cardiac index L./min./M.² BSA	Pulse rate	Mean arterial pressure mm. Hg	Left ventricular stroke work index Gm. M./beat/M.²
G. B.	1.86	.15*	94	12.76	12.00	4.48	72	93	78.6
44, M.		.14†	81	12.00	9.78	4.28	75	92	71.3
G. F.	2.05	.27*	83	13.61	11.30	3.12	87	90	43.9
32, M.		.26†	86	12.39	10.65	2.81	98	91	35.6
G. B.	2.12	.30*	84	10.58	8.89	3.44	82	100	57.1
38, M.		.29†	85	10.07	8.56	3.02	76	100	53.8
J. E.	2.08	.19*	112	10.72	12.01	3.83	88	90	54.2
39, M.		.08†	92	10.58	9.73	2.99	80	85	44.7
E. P.	2.02	.25*	81	12.90	10.44	3.38	94	93	44.0
36, M.									
C. W.	1.75	.29*	83	10.60	8.79	4.15	84	83	55.8
37, M.									
J. S.	1.90	.23*	82	9.33	7.66	2.50	88	76	29.4
41, M.									
Mean		.24*	88	11.50	10.16	3.56	85	89	51.9
values		.19†	86	11.28	9.68	3.28	82	92	51.3
p			>0.10‡	>0.10	>0.10	>0.10	<0.02	>0.10	
values		>0.10§	>0.20	>0.05	>0.10	>0.20	>0.10	>0.20	

*Values after lipid meal.

†Values after heparin.

‡Values after lipid meal compared to fasting controls of table 1.

§Values after lipid meal compared to values in same patient after heparin.

crements. These heparin effects appear dependent on the lipemia-clearing property, for no alteration in coronary dynamics was found in 6 additional patients in whom this activity was not manifest after the same heparin dosage.

The residual lactescence after post-heparin lipolysis was associated with no significant deviation of coronary dynamics from the normal. That a concentration-dependent phenomenon is operative, was confirmed in a separate group of patients in whom low lactescence values developed in the course of alimentary lipemia without affecting myocardial oxygen consumption.

The relevance of the lipemic state, per se, to the pathophysiology of myocardial ischemia appears to depend upon the establishment of an oxygen gradient within the myocardium, presumably through altered pressure-flow relationships produced by lipemic blood within a pathologic vessel.

Acknowledgment

The authors wish to acknowledge the technical assistance of Miss Virginia Everett and Miss Margaret Reese and the secretarial services of Mrs. Shirley Loy.

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The study of nature will ever yield us fresh matter of entertainment, and we have great reason to bless God for the faculties and abilities he has given us, and the strong desire he has implanted in our minds, to search into and contemplate his works, in which the farther we go, the more we see the signatures of his wisdom and power, everything pleases and instructs us, because in everything we see a wise design. And the farther researches we make into this admirable scene of things, the more beauty and harmony we see in them: and the stronger and clearer convictions they give us, of the being, power and wisdom of the divine Architect, who has made all things to concur with a wonderful conformity, in carrying on, by various and innumerable combinations of matter, such a circulation of causes and effects, as was necessary to the great ends of nature.—STEPHEN HALES, B.D., F.R.S. *Haemastatics.* Ed. 3, Dedication, p. vi.

An Appraisal of the Double Indicator-Dilution Method for the Estimation of Mitral Regurgitation in Human Subjects

By WILLIAM S. WILSON, M.D., RALPH L. BRANDT, M.D., RICHARD D. JUDGE, M.D., JOE D. MORRIS, M.D., AND MARY E. CLIFFORD, M.D.

THE shape of an indicator-dilution curve is determined by at least 4 variables: cardiac output, the volume between the injection site and the sampling site, the presence of a left-to-right intracardiac shunt, and the presence of valvular regurgitation.[1-3] In the absence of an intracardiac shunt and valvular regurgitation, one can predict the downslope of the arterial dilution curve, using the calculated values of cardiac output and "central blood volume." Several investigators have tried to estimate the amount of regurgitation in man by measuring the deviation of the observed downslope from the predicted downslope.[4-7] Lange and Hecht[8] have presented evidence suggesting that an estimate of mitral regurgitation may be obtained by comparing the dilution curves recorded simultaneously from the pulmonary artery and the femoral artery. There is evidence from studies on dogs with simulated valvular regurgitation that supports the validity of this technic.[9, 10]

This is a report of the results of the double-dilution-curve technic in the estimation of mitral regurgitation in 50 patients.

Materials and Methods

Fifty adult patients were studied during right heart catheterization. Indocyanine dye (5 to 12.5 mg.) was injected in an antecubital vein; the dilution of indicator at the pulmonary artery and the femoral artery was measured by drawing a continuous sample from each site through a cuvette oximeter at a rate of 32 ml. per minute. The proximal sample was drawn from the right ventricle in 2 patients in whom it was not possible to enter the pulmonary artery. The output of each oximeter was simultaneously registered on a cathode-ray photographic recording system* at a paper speed of 5 mm. per second. The downslopes of the curves were extrapolated after they were replotted on semi-logarithmic paper. The regurgitant flow, expressed as a fraction of the effective forward flow (Q_R/Q_F), was calculated by means of the equation derived by Lange and Hecht.[8]

$$Q_R/Q_F = \frac{(\triangle MCT - \triangle AT) - 0.6}{\triangle AT}$$

in which $\triangle MCT$ = time (seconds) between mean circulation times of two curves
$\triangle AT$ = time (seconds) between appearance times of the two curves

The amount of mitral regurgitation in each patient was also estimated by the use of a combination of other criteria. Each patient was examined by one or more of the authors and the degree of mitral regurgitation was estimated on the basis of the physical examination, the electrocardiogram, and the x-ray findings. Patients with aortic regurgitation were excluded. Twenty-six patients had percutaneous left atrial puncture by the method of Bjork and co-workers,[11] and an estimate of the relative importance of mitral regurgitation was made by dividing the extent of the y descent in the first 0.1 second by the mean left atrial pressure.[12] Twenty-three patients had operative exploration of the mitral valve.

On the basis of all available information, exclusive of the indicator-dilution curves, the degree of regurgitation was graded in each of the 50 patients (table 1).

Results and Discussion

The ratio of regurgitant flow to forward flow (Q_R/Q_F) varied from 0 to 2.43. There was usually a marked difference between the curves recorded from patients with little or no regurgitation and the curves recorded from patients with severe regurgitation. The similarity between the pulmonary and femoral arterial dilution curves recorded from a patient with slight regurgitation (group 1) is illustrated in figure 1. The curves recorded from a patient with severe mitral regurgita-

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Supported in part by the Dean's Fund of the Michigan Heart Association.

*Electronics for Medicine, White Plains, New York.

Table 1

Classification of Patients

Group	Number	Diagnosis		Method of Grouping	
0 (No regurgitation)	18	10	No heart disease	Clinical	
		7	Rheumatic heart disease	Operative Clinical	5 2
		1	Heart failure of indeterminate etiology	Clinical	1
1 (Slight regurgitation)	15	14	Rheumatic heart disease	Operative Clinical	11 3
		1	Subaortic stenosis	Autopsy	1
2 (Moderate regurgitation)	11	10	Rheumatic heart disease	Operative Clinical	5 5
		1	Heart failure of indeterminate etiology	Clinical	
3 (Severe regurgitation)	6		Rheumatic heart disease	Operative Clinical	2 4

tion (group 3) are shown in figure 2. The decrease in the maximum concentration and the more prolonged downslope in the femoral artery curve were consistent features in patients with severe regurgitation.

The amount of regurgitation estimated from the clinical and surgical data is plotted against the Q_R/Q_F from the dilution curves in figure 3. The relationship is not a perfect one, but it is significant that only 1 patient with moderate (grade 2) or severe (grade 3) regurgitation had a Q_R/Q_F ratio below 0.40.

The 6 points marked by x in figure 3 are of special significance in that each point represents a discrepancy between the estimate of the regurgitant flow by the dilution technic and the estimate of the amount of regurgitation by clinical and operative means. The one discrepancy in group 0 (Q_R/Q_F 0.97) had severe heart failure with no evidence of valvular disease; the etiology was obscure after intensive study, including right and left heart catheterization. There were 3 patients in group 1 with high Q_R/Q_F ratios. The patient with a Q_R/Q_F 0.90 had shown little improvement following a mitral valvulotomy and had clinical evidence suggesting a mixed lesion with predominant stenosis. It is possible that this patient may need to be reclassified into another group after re-operation. Another patient ($Q_R/Q_F = 0.71$) had autopsy evidence of severe subaortic stenosis but no valvular disease. The third exception in group 1 ($Q_R/Q_F = 2.0$) had good clinical evidence of severe predominant mitral stenosis. This impression was confirmed at operation, and only a minimal regurgitant jet was present. The patient had marked sustained improvement following the correction of the mitral stenosis. The one patient in group 2 with an unusually high regurgitant ratio (Q_R/Q_F 1.68) had heart failure of indeterminate etiology. A moderately loud systolic murmur was present at the apex, and on the basis of this rather tenuous evidence the patient was classified as group 2. The relatively low level of confidence in the classification of this patient makes it difficult to be certain regarding the cause of the discrepancy in this instance. The other discrepancy in group 2 was in a patient in whom the calculated regurgitant ratio seemed unusually low (Q_R/Q_F 0.20). All studies in this patient, except the dilution curves, indicated moderate mitral regurgitation: loud systolic murmur, evidence of left ventricular hypertrophy on physical examination and on the electrocardiogram, and a left atrial pressure pulse in which the ratio $\frac{Ry\ (0.1\ \text{sec.})}{\text{mean pressure}}$ was over 0.6.

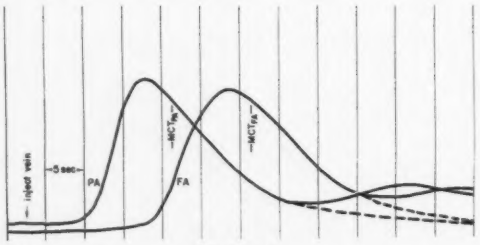

Figure 1

Pulmonary and femoral artery dilution curves from patient with severe mitral stenosis and minimal (grade 1) mitral regurgitation.

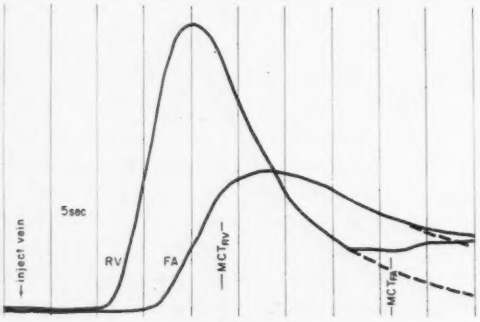

Figure 2

Right ventricle and femoral artery dilution curves from patient with severe mitral regurgitation.

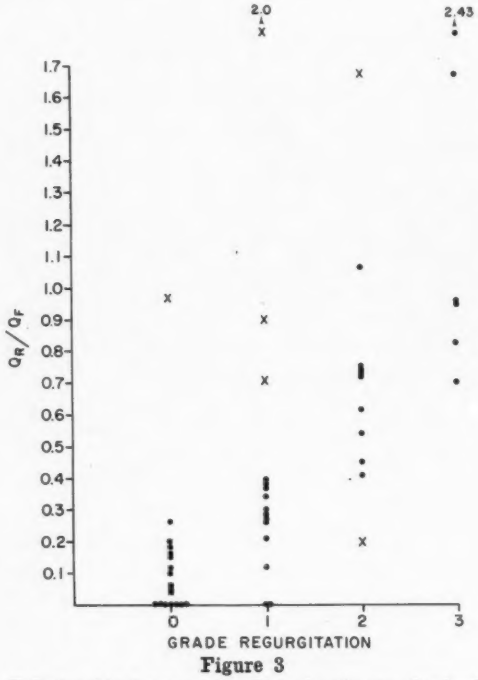

Figure 3

Relationship between the clinical estimate of mitral regurgitation and the estimate from the dilution curves.

It seems almost certain that the double-dilution technic provided a gross overestimate of the amount of regurgitation in the patient with subaortic stenosis (group 1, Q_R/Q_F 0.7), and in the patient with severe mitral stenosis (group 1, Q_R/Q_F 2.0). It is probable, although not so certain, that the amount of mitral regurgitation was overestimated by the double-dilution technic in 2 other patients (group 0, Q_R/Q_F 0.97; group 1, Q_R/Q_F 0.90). It is significant that each of these 4 patients had unusual enlargement of the left side of the heart; this is demonstrated in figure 4, an angiocardiogram showing a giant left atrium in the patient with operatively proved mitral stenosis and a Q_R/Q_F of 2.0.

The two other discrepancies between the two estimates of regurgitation (group 2, Q_R/Q_F 1.68 and 0.20) are less extreme, and the reasons for them are obscure at the present time. They may be due to errors in the grouping of the patients. It is possible that these discrepancies may be related to changes in the degree of mixing of the regurgitated indicator in the receiving chamber or changes in the distensibility of the receiving chamber.[13]

These data are interpreted as indicating that there are at least two factors that may alter the shape of an indicator-dilution curve after its formation in the pulmonary artery: left-sided valvular regurgitation and the presence of a large volume between the pulmonary artery and the femoral artery. In patients without great left-sided enlargement the effect of volume is insignificant, and the equation $\frac{(\triangle MCT - \triangle AT) - 0.6}{\triangle AT} = Q_R/Q_F$ is equal to a figure near zero in the absence of mitral or aortic regurgitation. The pulmonary and femoral arterial dilution curves become more dissimilar as the degree of mitral regurgitation increases, and the equation provides a

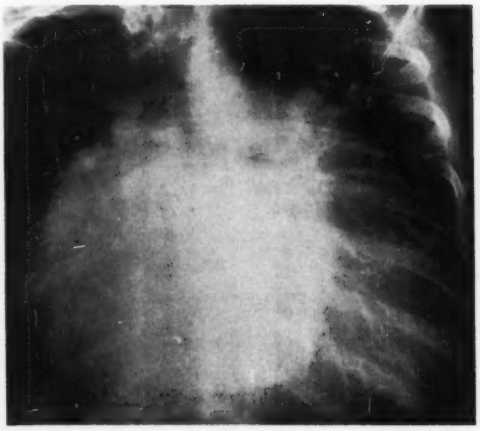

Figure 4

Angiocardiogram in patient with severe mitral stenosis and minimal mitral regurgitation (grade 1) showing large volume left atrium.

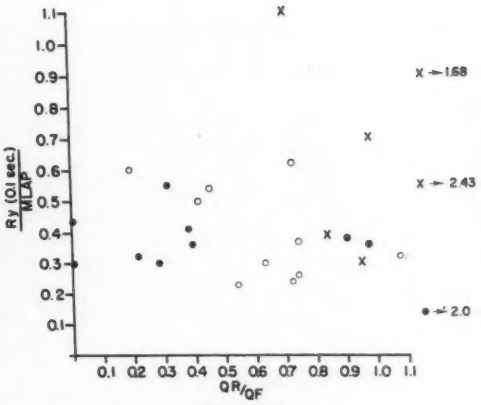

Figure 5

Relationship between calculated regurgitant ratio and the analysis of the left atrial pressure pulse. "x" denotes patients with severe regurgitation; patients with moderate regurgitation are shown as open circles; patients with no regurgitation or minimal regurgitation are depicted by solid circles.

clinically useful estimate of the amount of regurgitation. This information may be of great value in the selection of patients for surgical treatment, since patients with more than slight regurgitation are probably best treated by open valvulotomy with the extracorporeal pump-oxygenator, rather than by conventional mitral valvulotomy.

A comparison of the results with the double-dilution technic and the ratio

$$\frac{Ry\ (0.1\ \text{sec.})}{\text{mean left atrial pressure}}$$

described by Morrow and associates[12] for each of the 26 patients who had left atrial catheterization is illustrated in figure 5. The correlation with the degree of regurgitation was substantially less impressive with the pressure method than with the dilution method.

The effect of an unusually large volume between the pulmonary artery and the femoral artery may be a cause of falsely elevated regurgitant ratios and therefore limits the value of the double-dilution technic. There is experimental evidence indicating that a large volume between the pulmonary and femoral artery would be the dominant factor in determining the downslope of the femoral artery curve and would thus produce differences between the pulmonary artery and femoral artery curves in the absence of valvular regurgitation.[14]

Summary

The amount of mitral regurgitation was estimated in 50 patients by an indicator-dilution technic and by the usual clinical, catheterization, operative, and autopsy criteria. There was a good correlation between the two estimates. Patients with significant mitral regurgitation (grade 2 or grade 3) had, with one exception, Q_R/Q_F ratios above 0.41. There were at least two instances where the calculated Q_R/Q_F was almost certainly falsely high. It seems likely that these discrepancies are related to the presence of an unusually large volume between the pulmonary artery and the femoral artery.

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Though we can never hope to attain to the complete knowledge of the texture, or constituent frame and nature of bodies, yet may we reasonably expect by this method of experiments, to make farther and farther advances abundantly sufficient to reward our pains. And though the method be tedious, yet our abilities can proceed no faster; for as the learned author of the *Procedure of Human Understanding* observes, "All the real true knowledge we have of Nature is intirely experimental, insomuch that, how strange soever the assertion seems, we may lay this down as the first fundamental unerring rule in physics, *That it is not within the compass of human understanding to assign a purely speculative reason for any one phaenomenon in nature.*" So that in natural philosophy, we cannot depend on any mere speculations of the mind: we can only with the mathematicians, reason with any tolerable certainty from proper *data*, such as arise from the united testimony of many good and credible experiments.—STEPHEN HALES, B.D., F.R.S. *Haemastatics.* Preface, Vol. II, London, 1733.

Relationship between the Electrocardiogram and the Position of the Heart as Determined by Biplane Angiocardiography

By WARREN G. GUNTHEROTH, M.D., CARL-OLOF OVENFORS, M.D., AND DANAE IKKOS, M.D.

OVER 50 years ago, Waller pointed out the obvious correlation between anatomic and electrical phenomena, the mirror image electrocardiogram in situs inversus.[1] Shortly thereafter, Einthoven described other correlations between the position of the heart and the mean electrical axis in normal human subjects.[2] These correlations were extended to hypertrophied hearts by Groedel and Moncke-berg in 1913, who attributed marked shifts in electrical axis to rotation of the heart on its longitudinal axis.[3] Animal experiments followed,[4, 5] demonstrating that artificially produced rotations of the heart could cause more or less predictable changes in the mean electrical axis in the frontal plane.

The introduction of precordial leads, and the concepts of "unipolar" electrocardiography led to additional inferences of anatomic position from the electrocardiogram. Wilson considered that the "unipolar, semi-direct" chest leads recorded preponderantly local activity, permitting mapping of the anterior surface of the heart, and recognition of typical "right and left ventricular potential patterns."[6, 7] Subsequent authors stated that the interventricular septum could be located from the QRS transition zone in the precordial leads.[8–11]

The similarity of the right and left precordial leads to V_L and V_F in certain cases became the basis of Wilson's "electrical positions."[6] These, and the more literally anatomic positions of Goldberger,[12] Gardberg and Ashman,[13, 14] were based explicitly on extensive rotations of the heart about two or three anatomic axes.

In spite of the autopsy study by Grant, in 1953, demonstrating that rotations of the heart around its longitudinal axis rarely occur,[15] textbooks of electrocardiography continue to explain many electrocardiographic changes in normal and hypertrophied hearts on the basis of rotations,[9–12, 16–18] and the current literature contains literal inferences of anatomic position from the electrocardiogram.[19]

We therefore undertook to study in living subjects: (1) the extent of rotations of the heart occurring spontaneously, and (2) the correlation of these rotations with the mean electric axis in the frontal plane, and with the location of the QRS transition zone in the precordial electrocardiogram.

Material and Method

Fifty-three patients were selected from a series of 100 consecutive cases undergoing selective angiocardiography at the pediatric clinic of the Karolinska Sjukhuset, Stockholm. The remaining patients were excluded prior to knowledge of the electrocardiographic data, because of inadequate filling of one of the ventricles. The ages ranged from 1 to 18 years, with an average of 7.3 years. Because all but two of the patients had congenital heart disease, right ventricular hypertrophy was frequent. Table 1 gives the ages and diagnoses of the patients included in this study. Only one of the 53 individuals demonstrated right bundle-branch block with QRS of over 0.11 second, and 5 additional patients showed a QRS duration of just 0.10 second. Nine subjects had a QRS duration in excess of 2 standard deviations from mean, for their respective ages.[20]

The subjects all underwent cardiac catheterization followed by selective angiocardiography, as described by Kjellberg, Mannheimer, Rudhe, and Jonsson.[21] The contrast medium was injected into the right ventricle, except in the patients with coaretation of the aorta, in whom the injection

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Assisted by a grant (no. H-3998) from the U. S. Public Health Service.

Presented in part at the Thirty-first Scientific Sessions of the American Heart Association in San Francisco, October 24, 1958.

Table 1

Patient Data

Diagnosis	Age	Electrocardiographic axis	Anatomic axis (Degrees)	Septal axis	Transition zone (V-lead position)	Septum (V-lead position)
ASD + ITPV	18	+ 60	+40	0	5	5-6
VSD + PVO	15	+130	+35	0	2	5-6
IPS	10	−120	+50	+10	1-2	5-6
TF	9	+195	+30	+ 5	5	5-6
ASD, 1°	5	— 65	+50	+10	3	6-7
VSD	5	+ 60	+50	+40	4	2-3
COARCT.	4	+ 60	+45	+15	2-3	3-4
TF	3	− 90	+30	−20	2-3	6
VSD + PVO	1	+ 90	+40	+15	1-3	3-4
TF	1	+130	+15	0	1	5-6
CTPV	8	+140	+50	− 5	5	6-7
VSD	1	R=S	+50	+15	3-4	6-7
VSD	2	+ 30	+50	+15	3	2-3
PDA + AS	3	+ 70	+20	+10	4-5	4-5
PF	3	+110	+35	+10	2	5-6
ASD	2	+ 90	+35	0	2-4	5
ASD	4	+110	+40	+10	3-4	3-5
VSD	11	+ 90	+45	0	3-4	4-5
VSD + PFO	10	+ 80	+35	+ 5	2	4-5
VSD + PS	8	+ 65	+35	+20	2-4	4-5
IPS	9	+ 30	+45	+20	4	3-4
VSD	6	+ 70	+45	−10	3-4	3-5
VSD	9	+ 95	+70	0	1-3	2-3
IPS	10	+180	+65	+15	2-3	2-3
VSD	3	+ 75	+60	+15	2-3	2-3
TRUNCUS A	1	+ 50	+95	+10	1-2	5-6
VSD	16	+ 80	+50	+10	3-4	4-5
VSD	5	+ 60	+30	+ 5	2	4-5
TGV	3	−105	+50	+10	3-4	5-6
IPS	10	+100	+70	+10	2-4	4-5
VSD	12	+ 95	+40	+15	2-4	4-5
PVO, 1°	11	+105	+55	0	2-4	4-5
TF	10	+110	+20	0	3	6-7
VSD + PDA	5	+100	+40	−20	2-4	4-5
VSD	1	+ 90	+55	+ 5	3-4	6
COARCT	13	+ 30	+40	+10	3	1-2
PS, ASD, TS	9	+130	+50	0	2-5	4-5
IPS	10	+130	+55	+10	2-3	4-5
TF	10	+105	+40	+ 5	2-3	5
COARCT	6	+ 30	+55	+20	3-4	4-5
A-V COM	9	+ 60	+40	0	2-4	4-5
PA STEN	6	+ 90	+80	+10	2-3	4-5
TF	10	+145	+25	+10	2-4	5
COARCT	7	+ 70	+50	+10	4	2-3
TF	3	+110	+30	+ 5	2-4	5-6
PS INF	8	+110	+45	0	2-4	5
PDA + COARCT	10	+ 90	+50	+ 5	3-4	3-4
TF	2	+ 70	+25	+10	2-4	4-5
PS INF	2	+ 90	+45	+30	2	3-5
VSD + PS	18	+120	+55	+10	2-4	5-6
NO HD	9	+ 70	+50	−10	2	5
NO HD	12	+ 60	+45	+10	2-3	3-4
VSD	7	+110	+50	− 5	2-4	3-5

AS, aortic stenosis; ASD, atrial septal defect, secundum type; ASD (1°), atrial septal defect, primum type; A-V COM, atrioventricularis communis; COARCT, coaretation of the aorta; CTPV, complete transposition of pulmonary veins; ITPV, incomplete; IPS, isolated pulmonic stenosis; HD, heart disease; PDA, patent ductus arteriosus; PF, pentalogy of Fallot; PA STEN, stenosis of pulmonary artery; PVO, pulmonary vascular obstruction; PS INF, pulmonic stenosis, infundibular; TF, tetralogy of Fallot; TS, tricuspid stenosis; TGV, transposition of great vessels.

was made into the pulmonary artery. (The 5 subjects in the latter category included in this study were those in whom the catheter recoiled into the right ventricle, permitting visualization of that chamber.) An Elema film-changer was employed, allowing simultaneous exposure of 30 by 30 cm. frames in two perpendicular planes. All patients were studied in a supine position, in frontal, and true lateral projections, at 6 to 12 frames per second. The roentgen tube was 90 cm. from the plane of the film. Each exposure was indicated by a signal on an electrocardiographic tracing. Frames were selected in late diastole, coincident with the QRS complex, (fig. 1) and outlines of the two ventricles as they filled successively were traced onto the same paper, one for each projection. In the frontal projection, a line was drawn to divide the combined area of the two ventricles into equal parts. This line was designated as the anatomic axis, and when horizontal was defined as having 0° rotation in the frontal plane, and +90° when completely vertical (see fig. 2). These definitions conform to the terminology for the mean electric axis.

The plane of the interventricular septum was identified in both projections by the area of overlap of the two ventricular outlines. (When the septum was completely parallel to the frontal plane, it was evident as the narrow area *separating* the two ventricular outlines in the lateral view.) This plane, usually vertical, was projected toward the chest wall, and an estimate was made of the intersection of the septal plane with a line joining the conventional precordial electrode positions. The point of intersection was designated in terms of the nearest electrode position, to facilitate comparison with the location of the transition zone of the precordial electrocardiogram. Precise localization of the intersection of the septal plane and the thoracic wall was possible only when the septum was completely parallel to one of the two views.

Rotation of the septal plane could ordinarily be seen better from the lateral views. When the septal plane was completely vertical, septal rotation around its longitudinal axis was defined as zero degrees. Viewed from the apex of the heart, clockwise rotation was recorded in positive degrees, and counterclockwise rotation in negative degrees. Precision was limited by the geometry of the septum, a curved plane usually convex anteriorly. (In instances of marked right ventricular hypertrophy, however, the septum may be convex posteriorly).

In 28 patients, precordial electrodes from positions V_{4R} through V_7 were left in place after the conventional electrocardiogram was taken in the supine position, and "scout films" were taken in the two projections used for angiocardiographs, in the same position and on the same film-changer. In the remaining subjects, the electrode positions were deduced from thoracic landmarks (fig. 2).

The electrocardiograms were recorded on 5-inch photographic paper, at fast speeds, two to four leads simultaneously. The mean electrical axis was calculated from the standard limb leads I and III, by means of the Einthoven equilateral triangle. The QRS transition zone was designated as the precordial electrode position or positions at which it was recorded. (In all subjects, this zone lay between the positions V_{4R} to V_7). In addition, the first electrode positions were identified, which were definitely "right ventricular" type and "left ventricular" type, according to the definitions of Wilson.[7]

Results

The anatomic axis in the frontal plane ranged from +15 to +95°, with an average of +45°, and two standard deviations included ±29°. The mean electric axis, however, ranged a full 360°, with an average of +80°, and two standard deviations of ±125°. The correlation coefficient for the anatomic and electric axes was found to be far below values generally considered significant.*

A possible reason for poor correlation between anatomic and electric axes in the frontal plane is the rotation of the heart around its longitudinal axis. Therefore, the direction of the mean electric axis was compared with the degree of rotation of the septum. The septum showed relatively little rotation on its long axis, with an average position of +7° (slight clockwise rotation as viewed from the apex of the heart), and two standard deviations were included by ±21°. The correlation between septal rotation and mean electric axis was not significantly different from a chance correlation. (The calculated coefficient was –.189, which has a "p" value considerably greater than .05.)

Rotation of the heart in the transverse

*The correlation coefficient between mean electric axis and the anatomic axis for 52 subjects was —.126. (The fifty-third patient was not included in the analysis because his electrocardiogram showed equal R and S in all three limb leads, making estimate of the mean electric axis impossible). For 50 degrees of freedom, the correlation coefficient would have to be .273 to have a "p" value of less than .05 or .354 to have a "p" value of less than .01.

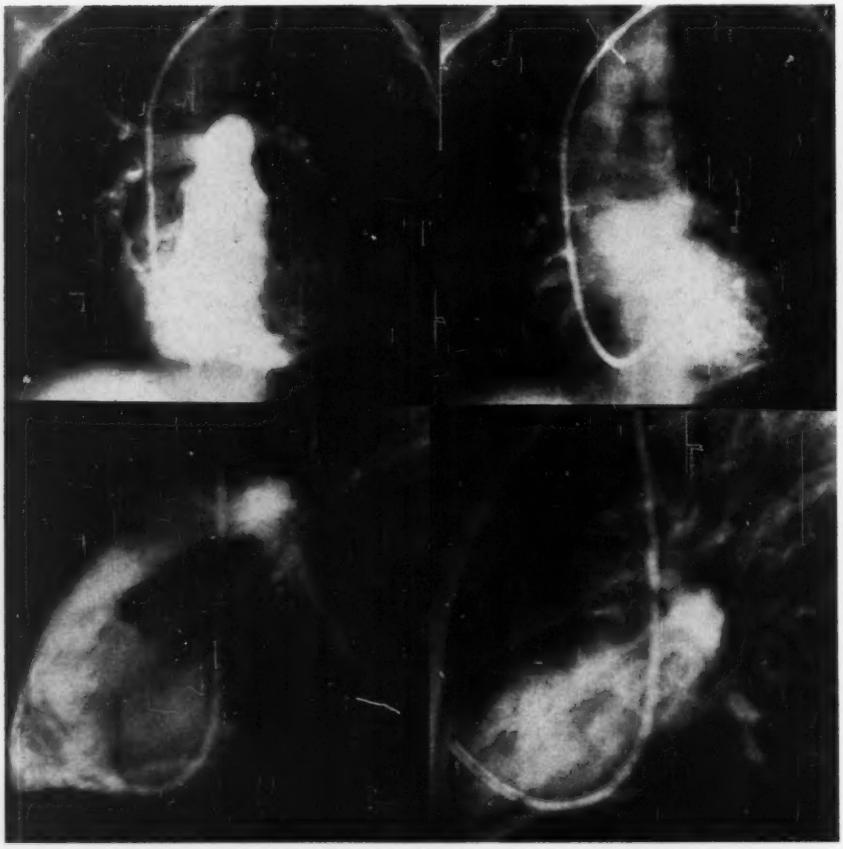

Figure 1

Angiocardiographs after injection of radiopaque material into the right ventricle. Top two frames are in anteroposterior projection; bottom are in true lateral projection. On the left, the right atrium, right ventricle, and pulmonary artery are filled. On the right, the pulmonary veins, left atrium, left ventricle, and aorta are filled.

plane was deduced from the intersection of the septal plane with the line joining the conventional precordial electrode positions. The anatomic position of the septum was identified in terms of the precordial electrode position nearest to this point of intersection. The mean position occurred between V_4 and V_5, and two standard deviations were included between V_3 and V_6. Electrically, the QRS transition zone occurred at V_3, for the mean, and two standard deviations were included between V_1 and V_5. The midpoint of each transition zone was correlated with the corresponding anatomic septal projection, resulting in a coefficient not significantly different from a random relationship ($r = .040$, $p > .05$). Similarly, correlating the first electrode position showing a "left ventricular pattern" with the first electrode anatomically over the left ventricle, failed to reveal a significant interdependence between these anatomic and electric variables. Similar results were found for the right ventricle.

The intersection of the septal plane with the thorax was correlated with the direction of the mean electric axis in the frontal plane.

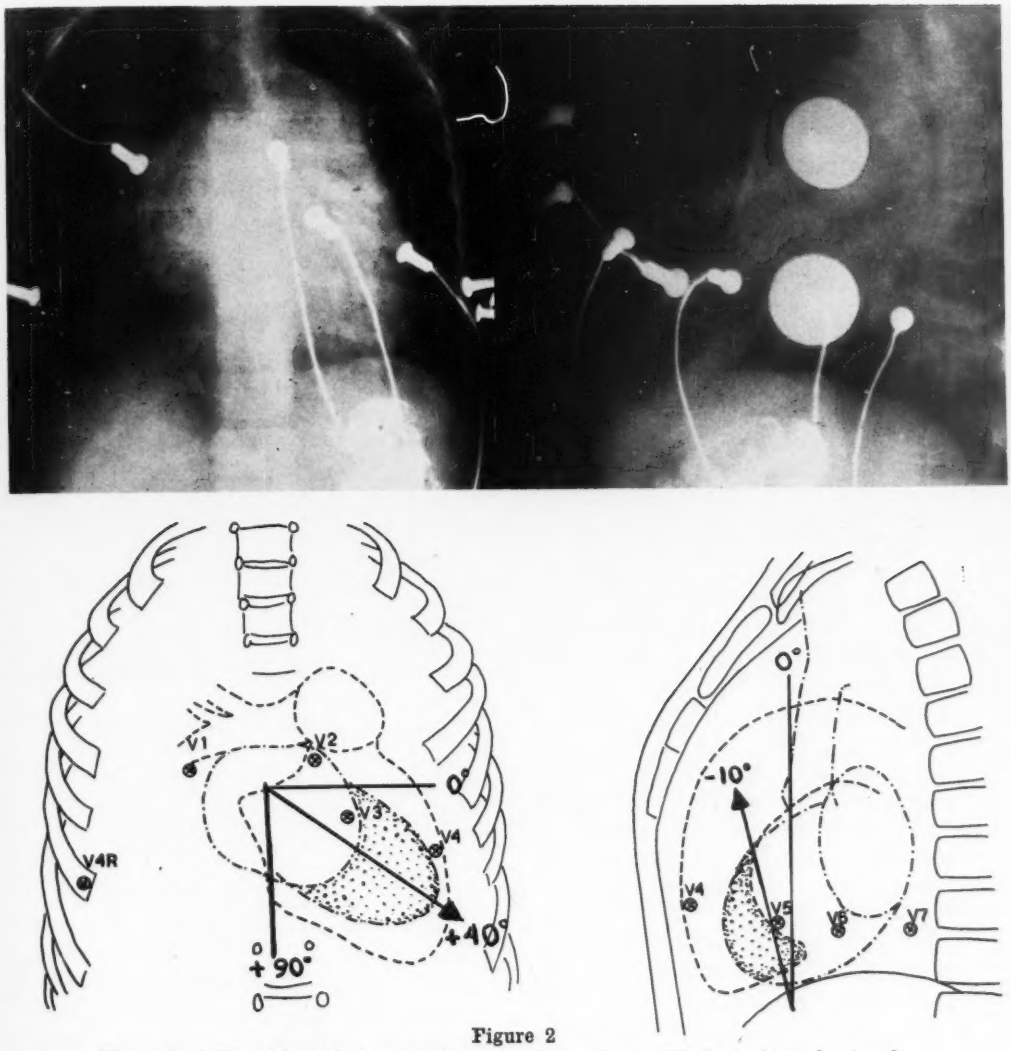

Figure 2

(Upper). A-P and lateral chest radiograms of a patient with chest electrodes in place. (Below). Electrode position superimposed upon the outline of the heart chambers. The interrupted line represents the right side, and the dot-dash line outlines the left heart. (N.B.: this is not the same patient represented in figure 1.) The shaded area represents the plane of the septum. The rotation of the anatomic axis in the frontal plane is +40°, in this case, and the septum demonstrates 10° of rotation, counterclockwise as seen in the lateral view.

The values indicated no important relationship between these variables (r = .034, $p > .05$).

One negative correlation was found that has important implications. When there was anatomic, clockwise rotation on the longitudinal axis, there was usually rotation of the heart toward the right in the transverse plane; i.e., the septal plane tended to intersect the chest wall further toward V_1 (r =

$-.313$; $p < .05$). This is in contradiction to a positive correlation assumed by several authors,[17, 18, 22] who have speculated that the interventricular septum is rotated toward the left precordium when the heart rotated in a clockwise fashion on its longitudinal axis.

Discussion

Rotation of the heart on its longitudinal axis was proposed initially by Groedel and Monckeberg as an explanation for the divergence of the mean electric axis in the frontal plane from the anatomic position of the heart in that plane.[3] These authors based their contention on a single autopsied case, in which they apparently mistook the normal anterior position of the right ventricle for clockwise rotation around the longitudinal axis. The excellent animal experiments by Boden and Neukirch[4] that followed were used as a basis for extrapolation to human electrocardiograms by literally generations of writers without demonstration of these rotations in human subjects, although the extent of rotations implied was considerable. Several authors even postulated that clockwise rotation could be so extreme that parts of the left ventricle would be subjacent to electrode V_1.[17, 22, 23]

Schwedel, in 1948, using posteroanterior radiograms of the chest, concluded that rotations around the longitudinal axis of the heart actually are quite limited in degree, usually less than 15°,[24] which is in good agreement with the findings of Grant[15] and of our own study. In animal experiments, Schweizer found that rotations within these limits produced no significant change in the mean electrical axis in the frontal plane.[25]

Rotation of the heart on its longitudinal axis was also assumed to explain various electrical phenomena of the precordial electrodes. Wilson introduced "electric positions," based upon resemblance of the "unipolar" limb leads V_L and V_F with the right and left precordial leads, to account for variations in the mean electric axis of the limb leads of normal subjects with normal precordial electrocardiograms: ". . . in normal subjects with right axis deviation, the potential variations of the right ventricular surface are transmitted to the left arm and the potential variations of the left ventricular surface to the left leg."[6] This explanation of the "vertical position," in which the QRS in V_L is similar to the QRS in V_1 and V_2, requires sufficient rotation of the heart around its longitudinal axis to allow V_L to "see" more of the right ventricle than the left.

Figure 3 is composed of photographs of a human skeleton with a model of a normal human heart (Model Number 1, American Heart Association). The heart was pierced with a steel rod in the plane of the septum, to approximate the anatomic axis. The left humerus was removed, and its attachment was left to assist in the visualization of the solid angle subtended by the heart from the position of lead V_L. The heart model is shown in maximal clockwise rotation in the frontal plane, maximal clockwise rotation around the longitudinal axis, and the median position for rotation in the transverse plane,* with respect to our 53 subjects, based upon two standard deviations. It is apparent that even with these extreme rotations, lead V_L does not "see" more of the right ventricle than the left, a condition required by Wilson's explanation of the "vertical electrical position."

The limits of rotation used in these photographs were found in patients with ventricular hypertrophy, and are probably in excess of those found in normal adults. Grant's precise study of the anatomic position of the heart in adults showed considerably less rotation in the frontal plane than occurred in our group, and he found "no instances of significant rotation of the heart around its longitudinal axis." Thus, the explanation of electric position based upon anatomic rotations is without logical foundation, either in normal subjects or in patients with ventricular hypertrophy.

*In the average position, the septal plane intersected the thorax between electrode positions V_4 and V_5. With maximal clockwise rotation around the longitudinal axis, the heart tended to rotate to the right in the transverse plane, and therefore caused the intersection of the septal plane to lie farther to the right in these circumstances.

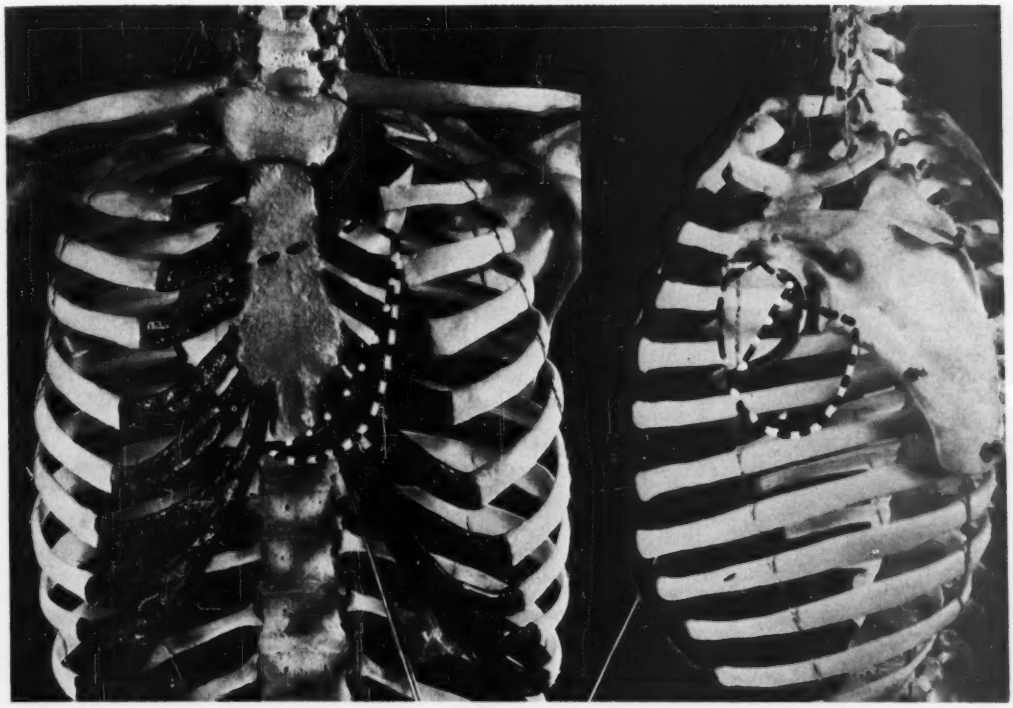

Figure 3

Model of a normal human heart, with maximal rotation in a clockwise direction in both frontal plane and around the longitudinal axis, comparable to Wilson's "vertical electrical position." The right ventricle is white, the left black. Photograph on the left "sees" the heart from the midline at the 4th intercostal space. Photograph on the right "sees" the two ventricles from the left shoulder; i.e., aV_L position. Even under these extreme rotations aV_L fails to "see" more of the right ventricle than left.

"Electrical positions," in conclusion, have no sound theoretical basis, are subject to the limitations of both dipole *and* unipolar theory and lack the quantitative advantage of Einthoven's mean electrical axis.[26] It is more logical, and direct, to describe the orientation in space of the heart's electromotive force in terms of right or left, anterior or posterior, and superior or inferior. Definition of the normal should be derived from statistical analyses and expressed in percentiles or standard deviations of normal, as has been done for other biologic variables such as height and weight.

Summary

Anatomic orientation of the heart was determined in 53 patients by selective, biplane angiocardiography, and was compared with the mean electric axis and the location of the transition zone from conventional electrocardiograms. No significant correlation could be demonstrated between (a) the anatomic axis and the electric axis in the frontal plane, or (b) between the electric axis and rotation of the heart about its longitudinal axis, or (c) the location of the interventricular septum and the transition zone of the precordial leads.

The electric variations are greater than can possibly be explained by known rotations of the heart about any anatomic axis.

The degrees of rotation about the heart's longitudinal axis assumed in the concept of "electrical positions" is beyond the range found in normal or hypertrophied hearts.

It is concluded that the electric positions of the heart should be abandoned in favor of direct description in three dimensions of the orientation of the mean electromotive force of the heart. Normal limits should be defined in percentiles or standard deviations.

Acknowledgment

This study was begun in 1954, during the tenure of an exchange fellowship between Children's Medical Center of Boston and the Karolinska Sjukhuset of Stockholm. Almost all the data were from patients examined by the team of Drs. Kjellberg, Mannheimer, Rudhe, and Jonsson; we gratefully acknowledge permission to use their material and their assistance in many other ways. Finally, we wish to acknowledge the assistance of Dr. Allen Scher, of the University of Washington, and Dr. Robert P. Grant, who offered many valuable suggestions in the preparation of this manuscript.

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Total Anomalous Pulmonary Venous Drainage at Cardiac Level

Angiocardiographic Differentiation

By R. D. Rowe, M.B., I. H. Glass, M.D., and J. D. Keith, M.D.

IN UNCOMPLICATED total anomalous pulmonary venous drainage, the commonest site of entry into the systemic venous circulation is through the left superior vena cava and the left innominate vein. In a diagnostically less spectacular group, comprising 30 per cent of all cases of the anomaly, the pulmonary veins enter the right atrium either directly or via the coronary sinus.[1] Whereas in the common, supracardiac type of connection diagnosis is usually simple, in those at cardiac level detailed anatomic definition may be extremely difficult.

It has been stated[2] that the contour of the heart in plain x-ray films of the chest is characteristic for total anomalous pulmonary venous drainage into the coronary sinus. In the experience of Bahnson et al.[3] and ourselves, this has not proved to be specific. Cardiac catheterization in both types of anomaly simply localizes a left-to-right shunt of large volume to the atrial level, demonstrates blood oxygen saturations of approximately equal values in all 4 chambers, moderate to marked pulmonary hypertension, and a patent foramen ovale or true atrial septal defect. Indicator-dilution curves of similar contour may be recorded after injections in all of the right heart chambers or tributaries, those following injection in the right ventricle and pulmonary artery having a longer appearance time than those after caval or right atrial injections.[4] A filling defect due to turbulence of contrast material at the site of insertion of the anomalous veins has been noted in venous angiocardiograms of patients in whom pulmonary veins enter the right atrium directly[5] but in a few children with the total anomaly, studied in this manner in the authors' laboratory, the sign was lacking.

None of these methods so far discussed has allowed differentiation of the two types of total anomalous pulmonary venous drainage at cardiac level. The purpose of this paper is to describe an angiocardiographic sign that permits such separation.

Material and Methods

Six cases of this anomaly, 4 with drainage into the coronary sinus and 2 with drainage into the right atrium directly, were studied. The patients were all young, 5 being under 6 months of age. The clinical, electrocardiographic, and radiographic features in all cases were compatible with total anomalous pulmonary venous drainage. Data from right- and left-sided catheterizations in each case prior to angiocardiography confirmed the presence of total anomalous pulmonary venous drainage at cardiac level. At the conclusion of the preliminary study, selective angiocardiography was performed with the catheter in the main pulmonary artery. An average amount of 1.6 ml. of contrast material (50 per cent, 85 per cent, or 90 per cent Hypaque; 70 per cent Diodrast) per Kg. of body weight was injected with use of technics and equipment previously described.[6] The diagnosis was confirmed subsequently at autopsy in 4 patients and at surgical correction in the remaining 2.

Results

In both groups a large pulmonary artery trunk and branches were visualized. Owing to the position of the catheter in 3 cases, only 1 major pulmonary artery branch was heavily opacified. It was in the outline of pulmonary venous return to the right atrium in the anteroposterior view usually between 1 and 2 seconds after the injection that the differences between the two types of connection were observed.

In the coronary sinus variety (fig. 1) pul-

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Aided by a grant from the Ontario Heart Foundation.

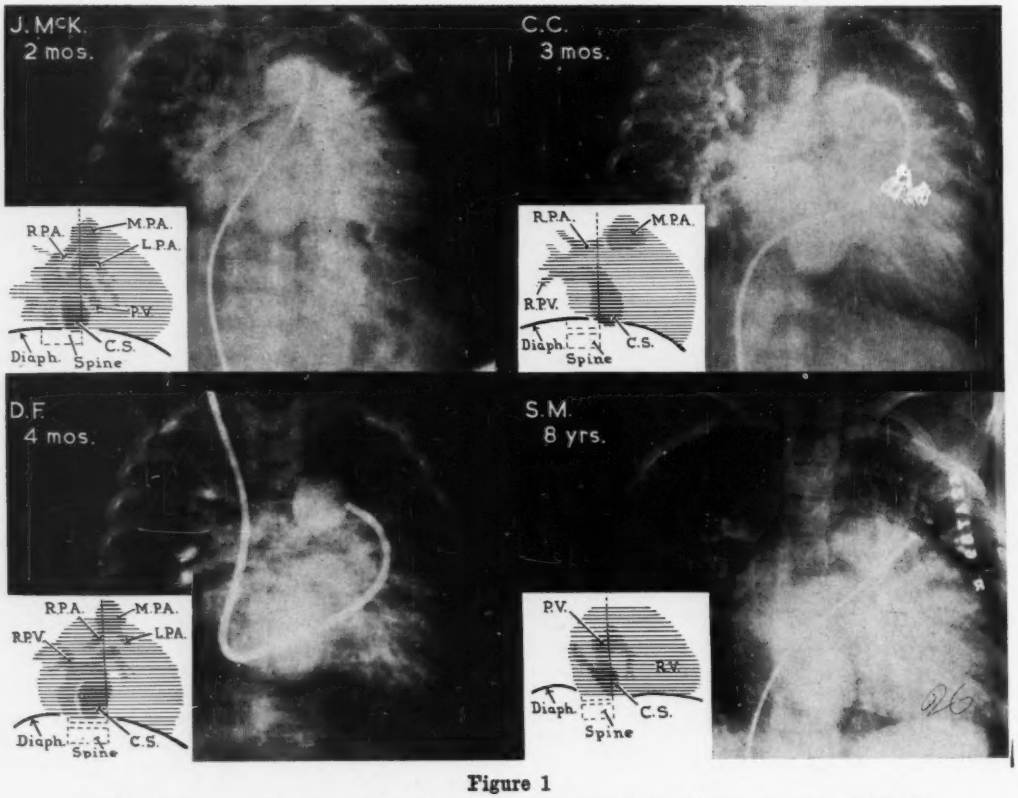

Figure 1

Selective angiocardiograms of 4 patients with total anomalous pulmonary venous drainage into the coronary sinus. Note in each instance an ovoid opacification within the right atrial segment.

monary veins from each lung merged into a common vein that arched upward to join its opposite and then descended into the coronary sinus. This latter structure opacified as a vertical, ovoid structure lying over the left side of the vertebral column with its lower margin at the level of the diaphragm. While quite obvious in very young infants, the appearance was more striking in the older patient and looked like an egg lying within the right atrium. The contrast gradually emptied into the right atrium proper, producing a faint opacification of that chamber.

Where all 4 pulmonary veins entered the right atrium directly (fig. 2) pulmonary veins appeared to pass in a horizontal manner at a lower level to form a circular opacity within the right atrium rather more to the right over the spine. The right atrium was more rapidly and completely filled with contrast than in the coronary sinus form.

In neither variety was the lateral projection contributory, nor did the presence of a true atrial defect rather than a foramen ovale appear to influence the degree of opacification of the coronary sinus or right atrium.

Discussion

As in so many cardiac anomalies, the final details of morphology depend in great part on a prior demonstration of the functional pathways of the abnormal circulation. Once it can be ascertained by preliminary cardiac catheterization that pulmonary venous drainage is totally anomalous and that the entry of these veins to the systemic system is at car-

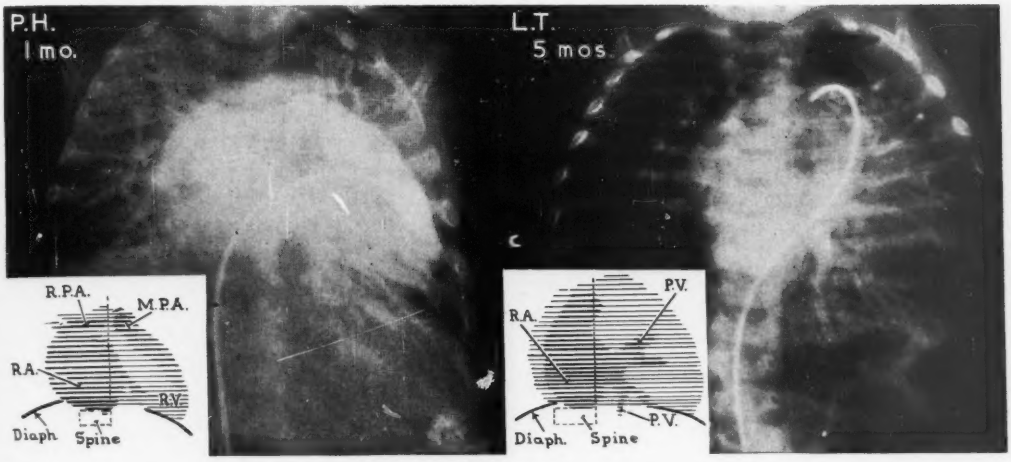

Figure 2

Selective angiocardiograms of 2 patients with total anomalous pulmonary venous drainage into the right atrium. Note in both instances, opacification of the right atrium but absence of the separate ovoid structure visible in the coronary sinus variety.

diac or atrial level, selective angiography will clarify the anatomic type of connection. Of the two types, the coronary sinus variety has the more arresting appearance after angiography. On the basis of present experience it is probable that this angiographic picture of the ovoid structure within the cardiac silhouette in this type is, under the named circumstances, a pathognomonic sign of the malformation. It seems likely from other evidence as yet unconfirmed, that when at least 2 pulmonary veins are connected with the coronary sinus in the mixed variety of total anomalous pulmonary venous drainage, a similar ovoid opacification can be demonstrated at angiocardiography.

When the pulmonary veins enter the right atrium by a final, single channel, as is usually the case, the angiographic appearance is also uniform though less striking. So far we have not demonstrated by this technic the less common examples of the right atrial connection having separate attachment of all 4 pulmonary veins. It may be possible to exclude such an arrangement when the pulmonary veins from either lung are seen to merge into a single vein before entering the right atrium.

With the advent of open-heart methods for their correction, the differentiation between total anomalous pulmonary venous drainage into the coronary sinus or right atrium has rather less practical importance than previously. Technically the coronary sinus variety is easier to repair whereas the type in which all 4 pulmonary veins are connected separately to the right atrium offers formidable surgical problems. Prior knowledge of the type may, therefore, still influence the timing of surgical treatment, especially in infants.

Summary

In 6 patients with total anomalous pulmonary venous drainage at cardiac level, differentiation between pulmonary veins entering the right atrium and those entering the coronary sinus was possible after selective angiocardiography into the pulmonary artery.

The principal feature of the angiocardiogram of the coronary sinus variety is an egg-shaped opacification over the spine within the right atrial contour. In the direct connection of pulmonary veins to the right atrium, the latter chamber may fill promptly after pulmonary venous return, sometimes starting as a circular shadow with the right

atrium but never having the ovoid appearance of the coronary sinus variety.

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As a frog's heart has but one ventricle, the blood is thrown by the same ventricle, at the same instant, both into the lungs and all over the body; then since its velocity is, in arteries of equal diameters, five times greater in the lungs than in the muscles, notwithstanding it is impelled by one common impetus; this evidently shows, that it must have freer passage through the lungs. Accordingly the left ventricle of the heart is made much stronger, thereby to impel the blood with a greater force than the right ventricle does.—STEPHEN HALES, B.D., F.R.S. *Haemastatics*, Vol. II, London, 1733.

Intracardiac Knotting of the Catheter during Right Heart Catheterization

By JOHN F. SKINNER, M.D., AND JOHN T. BURROUGHS, M.D.

SERIOUS complications of cardiac catheterization have been infrequent. They have included atrial arrhythmias, ventricular tachycardia, premature ventricular beats, ventricular standstill,[1] ventricular fibrillation,[2] pulmonary artery thrombosis,[3] and perforation of the heart.[4] In addition to these complications, knotting of the catheter has been rare. When knotting has occurred, it has been possible to withdraw the catheter from the heart and to deal with the knotted end in a peripheral vein.

In the case reported here the knot involved the chordae tendineae of the tricuspid valve, and an open cardiotomy was required to extricate the catheter.

Case Report

The patient, a 38-year-old white man, was admitted to Wadsworth General Hospital on October 20, 1959, because of shortness of breath and repeated episodes of congestive failure over the previous 9 months. Because of the possibility of a pulmonary arteriovenous fistula, right heart catheterization was done, primarily to perform selective dye-dilution curves.

A no.-8 Cournand single-lumen catheter was introduced into the left basilic vein and was passed into the right ventricle under fluoroscopic monitoring. Attempts at placing the tip of the catheter in the pulmonary artery were unsuccessful, for the catheter repeatedly knuckled; the tip remained in the right ventricle, while a loop passed into the pulmonary artery. At this time it was decided to substitute another catheter. As the catheter was withdrawn, the proximal loop disappeared. Clear visualization of the tip of the catheter was difficult because of the patient's obesity and superimposition of the tip of the catheter over the spine. When traction was made, there was tugging on the catheter synchronous with the heart beat. Fluoroscopic examination showed the tip of the catheter in the region of the tricuspid valve, but no knot was apparent. Several manipulations were attempted: these included advancing and withdrawing the catheter, clockwise and counterclockwise twisting, introduction of a Bing wire, and injecting saline rapidly with hopes that the jet fluid at the tip of the catheter would dislodge it. Attempts at introducing the catheter farther into the right ventricle were followed by runs of ventricular premature beats. Attempts at withdrawal also resulted in premature beats, and the patient complained of retrosternal pain.

Posteroanterior, lateral, and oblique films showed an overhand knot at the tip of the catheter near the tricuspid valve area (figs. 1 and 2). Further attempts were made to remove the catheter during observation with an image amplifier. These included considerable traction that raised the heart 4 to 5 cm. from the diaphragm. When all measures failed, it was concluded that the tip of the catheter was knotted in the chordae tendineae of the tricuspid valve, and that the only possibility of removal was by cardiotomy.

A right anterior thoracotomy with sternal transection was performed under hypothermia. Under purse-string suture control a finger was introduced into the right atrium through the atrial appendage. The knot in the catheter could be felt entangled in the chordae tendineae of the anteromedial commissure of the tricuspid valve, but extrication of the catheter by closed manipulation was not possible. Inflow was then stopped by occlusion of the venae cavae and the atrium was opened. The area of the tricuspid valve was well visualized, and a tight overhand knot in the tip of the catheter was seen. The catheter itself just proximal to the knot had become intertwined with a bundle of chordae just as one would twist 2 pieces of coarse wire together (fig. 3). The knot in the catheter prevented untwisting and traction only made the intertwining more firm. Ecchymosis of the adjacent papillary muscle was noted. The catheter was cut and removed, and the atrial incision was closed. Total circulatory occlusion was 3 minutes and 28 seconds. The patient's postoperative course was uneventful, and he was discharged from the hospital 3 weeks after surgery.

From the Departments of Cardiology and Thoracic Surgery, Wadsworth Veterans Administration Hospital, and the Department of Surgery, University of California Medical Center, Los Angeles, California.

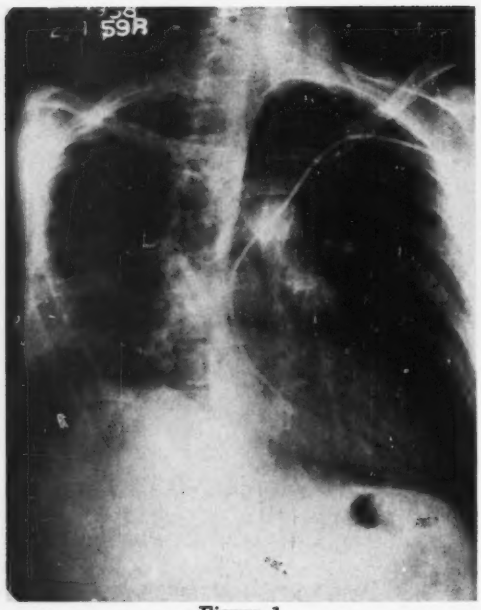

Figure 1

The right anterior oblique roentgenogram demonstrates a true overhand knot in the region of the tricuspid valve.

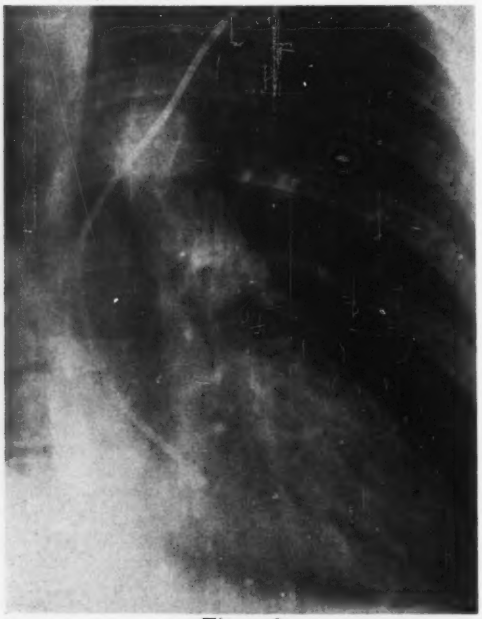

Figure 2

Enlargement of the right anterior obilque roentgenogram demonstrates more clearly the overhand knot at the tip of the catheter.

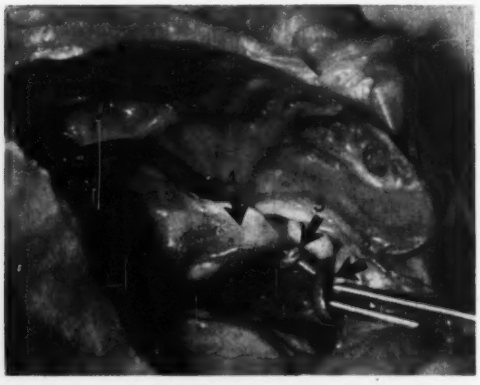

Figure 3

Photograph showing position of the knotted catheter emerging from the superior vena cava, crossing the right atrium, and becoming entangled in the tricuspid valve. 1, septal leaflet of the tricuspid valve; 2, overhand knot at the tip of the catheter; 3, loop of chordae tendinae around catheter. (This photograph was made for demonstration purposes on another human specimen in the autopsy room after removal of the anterior atrial wall.)

Discussion

Serious complications of cardiac catheterization have been infrequent. Cournand states that he has never experienced a similar complication.[5] Paul Wood described several instances during right heart catheterization when the catheter knotted but reduction was easily accomplished by moving the catheter to and fro.[6] Earl Wood has not had a similar complication but refers to 2 cases in which the cardiac catheters broke in two during the procedure. The catheters were smooth-bore Nylon catheters without a woven Nylon covering.[7] Bing has never had difficulty with the catheter knotting and entangling in the chordae, but he describes a case in which a true knot formed at the tip of the catheter that could be withdrawn into a peripheral vein.[8]

Not infrequently during the catheterization there is looping of the catheter in either the right ventricle or right atrium. These loops are usually seen by the fluoroscopist, and

manipulation of the catheter obviates knots. If true knotting of the catheter does occur, however, it is usually possible to pull the knot peripherally into the brachial vein, where it can be easily removed.

The catheterization procedure on this patient was performed with fluoroscopic monitoring. There was difficulty in seeing the catheter clearly because the patient was large and obese, and because the loop of the catheter overlay the thoracic spine. The catheter appeared to be unlooping as it was being withdrawn from the pulmonary artery, but apparently a tight overhand knot at the tip of the catheter was being formed. Presumably the catheter passed between the chordae tendineae of the tricuspid valve as it was being introduced into the right ventricle. When the catheter was withdrawn, the knot was drawn tight and would not pass between the chordae. Twisting the catheter in attempts at removal aggravated the problem by intertwining the catheter in the chordae.

There is no general agreement whether a rigid or flexible catheter should be used. Perforation of the right ventricle has been reported during right heart catheterization.[4] Because of this hazard Cournand is more concerned about rigidity than flexibility.[5] Soon after a catheter is introduced into the blood stream, the temperature of the blood causes softening of the catheter and it becomes more flexible. Frequently a second catheter must be used. Dexter comments that if catheters are very limp, they are far more traumatic and more prone to tie themselves into knots than are stiff catheters.[9] At the Peter Bent Brigham Hospital the cardiac catheters are hardened in the oven at 100 C. for 30 minutes with the catheter tip held in the desired curved position.

The etiology of the chest pain during the attempts to remove the catheter by traction is not known. It may have been produced by displacement of mediastinal structures, since there was shifting of the superior vena cava to the left when traction was applied and the heart was displaced upward. Ecchymosis of the papillary muscle was noted at time of cardiotomy, and it is possible that the chest pain was related to ischemia secondary to traction on the papillary muscle.

Summary

A complication of right heart catheterization is reported in which the catheter became knotted and entangled in the chordae tendineae of the tricuspid valve. Removal required open cardiotomy with hypothermia and temporary inflow occlusion.

Acknowledgment

We wish to acknowledge the advice of Dr. M. L. Pearce in the management of this patient and the composition of this report.

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Origin of Right Pulmonary Artery from Ascending Aorta

By C. A. Wagenvoort, M.D., Henry N. Neufeld, M.D., Richard F. Birge, M.D., John A. Caffrey, M.D., and Jesse E. Edwards, M.D.

A REVIEW of the literature reveals that origin of the right pulmonary artery from the ascending aorta is an extremely rare circumstance. The case reported by Ambrus[1] is believed to be an example of this congenital malformation. Recently a similar case has been described in a clinicopathologic conference at the Mayo Clinic by DuShane and associates.[2] To the best of our knowledge, the following description represents the third example of the entity in the literature. Special attention was paid to two features: (1) the histologic structure of the right pulmonary artery, which is believed to be formed in part by a right ductus arteriosus, and (2) the structure of pulmonary arterial branches and arterioles, which we studied in both lungs because the vascularization differed significantly in the two. The specimen described in the aforementioned clinicopathologic conference[2] was available for comparison of these features.

Report of Case

A white female infant was born to a 31-year-old primigravida. Pregnancy and hospital delivery had been uneventful, and the infant did well in the hospital. No cyanosis or distress was noted, and the infant was dismissed at the age of 5 days. During the following 2 weeks there was some difficulty with regurgitation and some irritability. On examination 10 days after dismissal no abnormalities of heart or lungs could be found. When 20 days old the patient suddenly died after feeding.

The relevant necropsy findings were confined to the heart, great vessels, and lungs. The heart was enlarged and showed right and left ventricular hypertrophy. All valves were normal, as was the atrial septum, except that there was a valvular-competent patent foramen ovale. The right ventricle gave rise to a large pulmonary trunk, which continued as a single wide pulmonary artery to the left lung (fig. 1*a*). No origin of the right pulmonary artery was found here. There was a short ductus arteriosus in the usual location, still patent but obviously in the process of closing. The aorta arose from the left ventricle. The arch was on the left side. The innominate artery, left common carotid artery, and left subclavian artery originated normally from the aortic arch. At the very base of the innominate artery a relatively long and thin right pulmonary artery originated from the ascending aorta (fig. 1*b*). Its lumen was narrow at the beginning and remained so for more than half of its length, but the distal portion was wide (fig. 2). The venous return to right and left atrium was normal. The right lung was large and markedly congested; the left lung was relatively small.

Histologically the ductus arteriosus on the left side presented the appearance usually found in the ductus shortly after birth: a thick media with a rather loose meshwork of elastic fibers, an internal elastic membrane, and a markedly thickened intimal layer. This layer, which in some areas had formed thick intimal cushions, was composed of a peculiar type of loose connective tissue with abundant collagenous fibers, relatively few elastic fibers, many smooth-muscle fibers, and much intercellular substance (fig. 3*a*. *b*, and *c*).

The structure of the long narrow portion of the right pulmonary artery was entirely similar to that described in the left ductus arteriosus, except that the media contained many thick elastic membranes (fig. 3*d* and *e*), just as did the distal part of the vessel. This latter portion had a normal appearance (fig. 3*f*), similar to that of the left pulmonary artery.

For studying the histologic structure of the pulmonary vascular tree, blocks were taken from 5 different segments of each lung. Sections of the paraffin-embedded blocks were stained with hematoxylin and eosin and with Lawson's elastic stain counterstained with van Gieson's.

A striking difference of thickness was found between the media of the muscular arteries in the right lung and that in the left. Quantitation was accomplished by the method described by Wagenvoort.[3] The thickness of the media is expressed as a percentage of the diameter of the vessel. Increase of the thickness may result from vasoconstriction or from hypertrophy; decrease may

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Supported in part by research grant H 3531 from the National Heart Institute, U. S. Public Health Service.

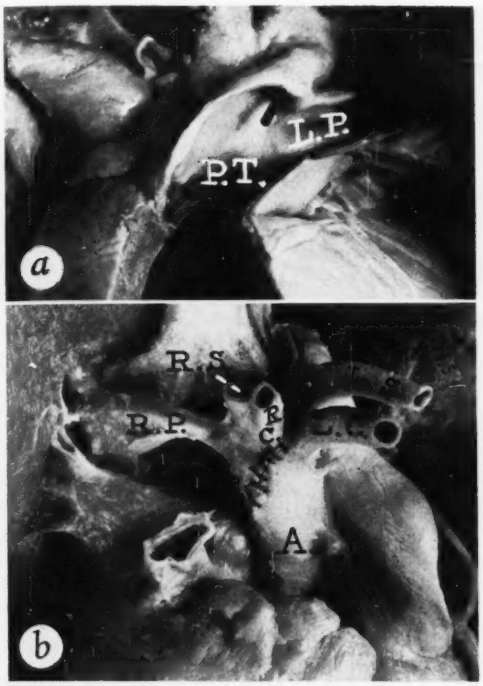

Figure 1

a. *Pulmonary trunk (P.T.) giving rise to left pulmonary artery (L.P.) but not to a right pulmonary artery. Probe in patent ductus arteriosus.* b. *Origin of stenosed right pulmonary artery (R.P.) from the ascending aorta (A.). R.S. = right subclavian artery; R.C. = right common carotid artery; L.C. = left common carotid artery; L.S. = left subclavian artery.*

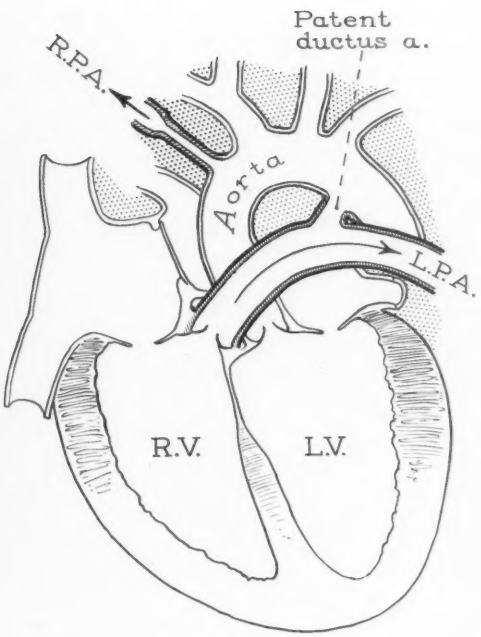

Figure 2

Heart and great vessels. Pulmonary trunk continued as left pulmonary artery and was connected with aorta by patent ductus arteriosus. Right pulmonary artery arose from ascending aorta near innominate artery and was stenotic for its greater part.

be due to atrophy or dilatation. In our case the mean percentage in the right lung was 4.4 (fig. 4*a*); but in the left, where the pulmonary arterial branches were very thick-walled, the mean percentage was 15.4 (fig. 4*b*).

In a further stage, the area of the cross-sectional surface of media is related to the area of lung tissue in the slides. The ratio between vascular muscle tissue and pulmonary parenchyma is indicative of medial atrophy or hypertrophy. In the right lung the index was 121, and in the left it was 447.* The percentage and the index are quantitative expressions of the very marked difference in the appearances of the vessels in the two lungs.

Besides the abnormality of the media, the pulmonary arterial tree of the right lung showed concentric intimal proliferation in many vessels (fig. 4*c*). This intimal change was not combined with the elastic proliferation and splitting of the internal elastic layer, as seen in pulmonary hypertension; but in some small arteries it was so extensive that it caused almost complete obliteration of the lumen (fig. 4*d*). In the left lung no intimal lesions could be found.

*Since the first report[3] of this technic, the last 2 digits of the index have been dropped for the sake of convenience. To obtain the actual surface area of the media, expressed in square microns per square centimeter of pulmonary tissue, the index as given here should be multiplied by 100π.

Discussion

It has been suggested[2] that origination of the right pulmonary artery from the ascending aorta might depend on abnormal development of the sixth aortic arch. A scheme of the aortic arches in a very early stage of development in the human embryo is given in fig. 5*a*. Of the original 6 pairs of arches, the third,

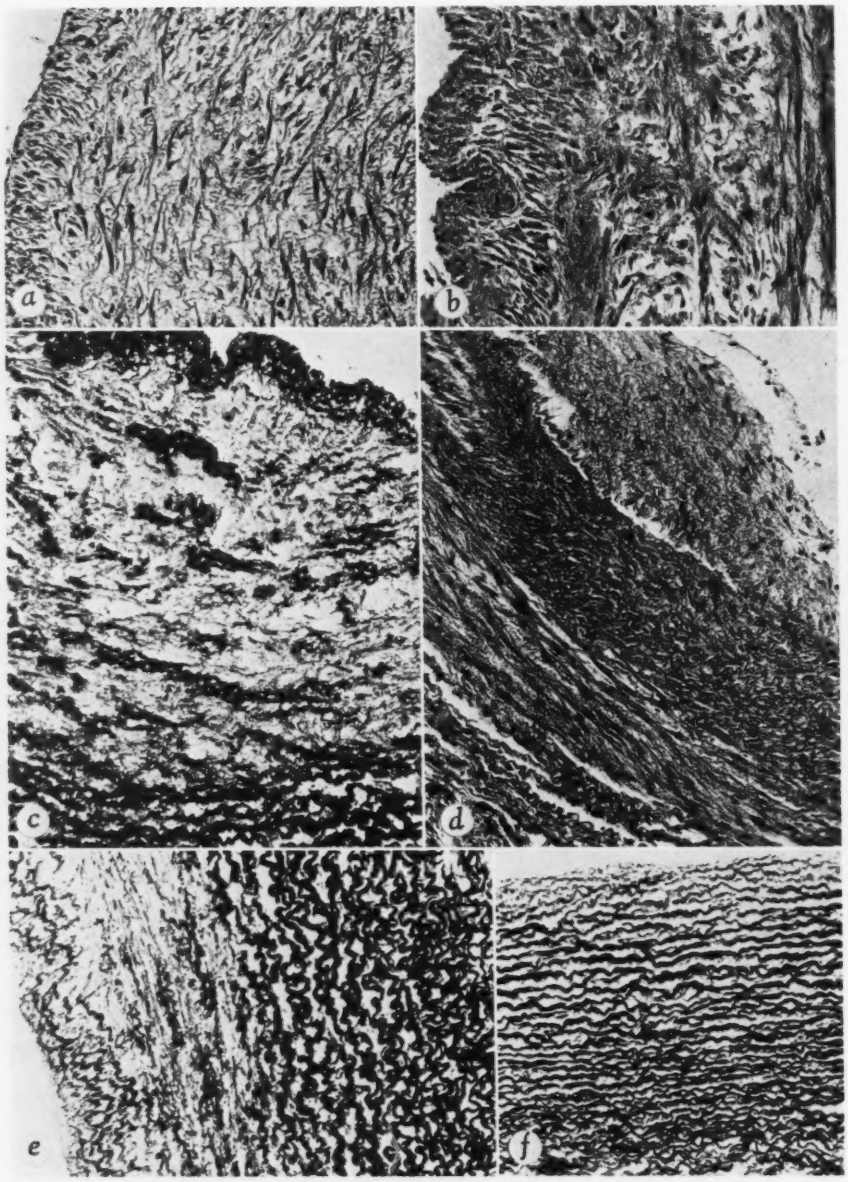

Figure 3

a. Intimal cushion in wall of left ductus arteriosus (hematoxylin and eosin stain). b. *Wall of ductus arteriosus, showing loose connective tissue and smooth-muscle fibers (hematoxylin and eosin stain).* c. *Wall of ductus arteriosus, showing much compact elastic tissue in outer layer though most of ductus wall contained relatively few elastic fibers, separated by loose connective tissue (elastic-tissue stain).* d. *Wall of proximal part of right pulmonary artery: media contained many smooth-muscle fibers and much intercellular substance; intimal cushions consisted mainly of loose connective tissue (hematoxylin and eosin stain).* e. *Wall of proximal part of right pulmonary artery: intimal*

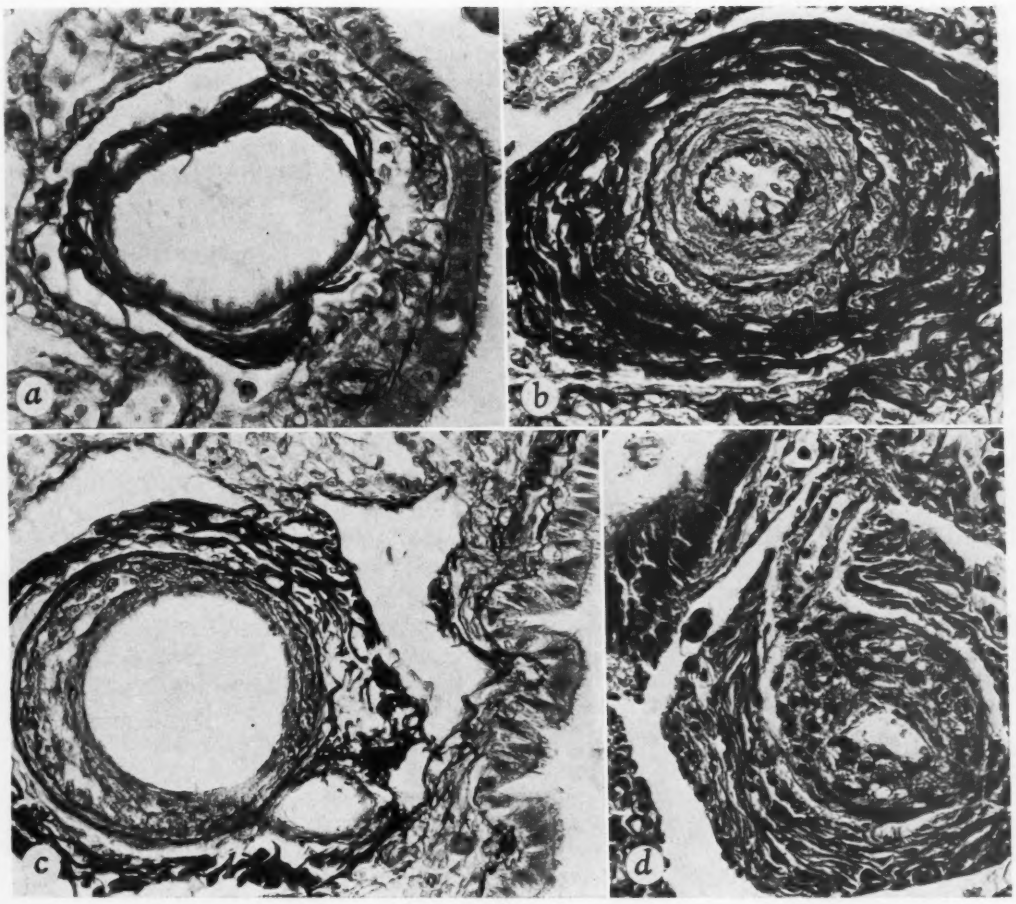

Figure 4

a. *Pulmonary arterial branch in right lung, showing very thin media (elastic-tissue stain).* b. *Pulmonary arterial branch in left lung, showing marked medial hypertrophy (elastic-tissue stain).* c. *Pulmonary arterial branch in right lung, showing very thin media but marked degree of concentric intimal proliferation (elastic-tissue stain).* d. *Pulmonary arterial branch of right lung, showing almost complete obliteration by intimal proliferation (hematoxylin and eosin).*

fourth, and sixth pairs remain, entirely or partly, as contributions to the definitive vascular system. The pulmonary arteries arise as branches from the corresponding sixth aortic arches. During normal further development the distal portion of the right sixth arch disappears, while the proximal part, in connection with the branch arising from the arch, forms the right pulmonary artery. On the left side normally the distal end of the sixth arch persists as the ductus arteriosus (fig. 5*b*).

When the distal end of the right sixth arch

cushions contained few elastic fibers; media contained many elastic membranes and resembled media of distal part of this artery (elastic-tissue stain). f. *Wall of distal part of right pulmonary artery, showing parallel dense elastic membrances as seen in cases of pulmonary hypertension and in normal newborn (elastic-tissue stain).*

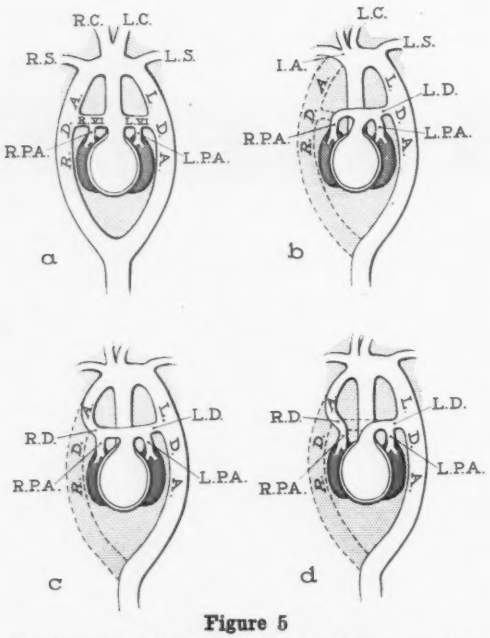

Figure 5

Development of origin of right pulmonary artery from ascending aorta. R.D.A., L.D.A. = right and left dorsal aorta; R.VI, L.VI = right and left sixth aortic arch; R.P.A., L.P.A. = right and left pulmonary artery; R.S., L.S. = right and left subclavian artery; R.C., L.C. = right and left common carotid artery; I.A. = innominate artery; R.D., L.D. = right and left ductus arteriosus. a. *Modification of early stages of normal in which right dorsal aorta and fourth and sixth pairs of aortic arches are present. The modification involves placement of subclavian arteries as shown, at a more cephalad level than sixth aortic arches. Normally subclavian arteries lie in caudad position at this stage, and shift later, by differential growth, to position shown in this diagram. From sixth arches, right and left pulmonary arteries have arisen. Common truncus arteriosus exists at this stage.* b. *Normal situation at time of birth. Right dorsal aorta and distal part of right sixth aortic arch have disappeared. Distal part of left sixth arch forms (left) ductus arteriosus.* c. *Persistence of part of right dorsal aorta and of whole right sixth arch. This situation represents double ductus arteriosus of type reported by Kelsey and associates.*[4] d. *Developmental bases for the malformation reported here—origin of right pulmonary artery from ascending aorta. Persistence of part of right dorsal aorta and of distal part of right sixth arch. Proximal part of this arch, however, has disappeared. Since a ductus arteriosus represents distal part of a sixth aortic arch, this case may be said to represent yet another form of double ductus arteriosus.*

fails to disappear, a symmetrical configuration of the great vessels eventuates with formation of an arcade (fig. 5*c*). This extremely rare situation, which indeed is a double ductus arteriosus, has been reported before.[4]

In our case it is supposed that the proximal part of the sixth arch (which normally persists) was interrupted, and that the distal end (which normally disappears) was retained. As a result the right pulmonary artery originated entirely from the aorta (fig. 5*d*). If this supposition is correct, the proximal part of the right pulmonary artery was formed by the right dorsal aorta, and the distal part by the branch from the sixth arch, whereas a central part was formed by a right-sided ductus arteriosus. For this reason our case also is considered an example of double ductus arteriosus.

Ambrus[1] believed that the right pulmonary artery in his case had developed as an anomalous branch from the fifth right aortic arch. Such an origin, however, seems not very likely, since the fifth pair of aortic arches in the human embryo are present during only a very short period and since normally only the sixth pair give rise to branches destined for the pulmonary circulation. No structures other than those which normally enter into the formation of the pulmonary arteries need be considered in explaining the developmental basis for the malformation here encountered.

The presence of typical ductal tissue in the proximal course of the narrowed right pulmonary artery gives strong support to the concept that in part this vessel is a ductus arteriosus. In the case reported by DuShane and associates,[2] which also was studied by us, we found ductal tissue in the left ductus arteriosus, as could be expected. The right pulmonary artery, which in that case was very wide, contained in the portion close to the aortic origin a marked intimal thickening consisting of loose connective tissue. Whether this also was ductal tissue or just a patch of intimal sclerosis could not be established.

An interesting aspect of the presently reported case was the structure of the pulmonary arterial branches, for the vascularization in the two lungs was entirely different. The cause of the intimal proliferation in several branches of the arterial tree of the right lung remains obscure. It did not resemble the intimal thickening with elastic proliferation seen in pulmonary hypertension, nor did it suggest organization of thrombi. No such proliferation was found in the left lung.

Also, the media of the muscular pulmonary arteries was markedly different in both lungs. The mean relative medial thickness in the right lung, 4.4 per cent, is very low for an infant of 3 weeks. In studying a group of lungs of normal infants we found[5] that in the age period of 2 to 5 weeks the mean medial thickness of the pulmonary arteries ranged from 8.0 to 12.8 per cent of the diameters of the vessels. In the present case the index of the medial surface area per square centimeter of lung tissue was 121 in the right lung, while in the control group the range was from 180 to 257. Therefore we have concluded that the pulmonary arterial tree in the right lung shows medial atrophy. We believe this atrophy is related to the almost complete obliteration of the right main pulmonary artery. Probably both the narrowing of the right pulmonary artery and the medial atrophy in its branches began during fetal life.

It should be noted, however, that the configuration of the elastic tissue in the wall of the right pulmonary artery was similar to that in the left, showing the structure characteristic of a fetal pulmonary artery. This observation suggests that the stenosis occurred rather late in fetal life. Otherwise the pulmonary arterial wall might have shown a more irregular pattern of the elastic fibers.[6] It seems likely that the narrowing in this case represents the normal closing of the right ductus arteriosus.

In the arteries of the left lung, however, the mean medial thickness was 15.4 per cent of the diameter of the vessels, and the index of the mean medial surface area per square centimeter was 447. In comparison with figures derived from normal lung vessels these quantities are very high and indicate medial hypertrophy. Since the left pulmonary artery was wide and was connected with the aorta by a patent left ductus arteriosus, we suppose that this medial hypertrophy is the expression of a persistent high pressure in the left pulmonary circulation.

As a parallel, the pulmonary vascular tree in the case of DuShane and associates[2] was studied in the same way. That patient had been 4 months old at death. Her condition had been identical with that of our patient, except that the right pulmonary artery, which also originated from the aorta, was not stenotic but widely patent throughout. As in our case, the ductus arteriosus was patent.

The mean medial thicknesses in right and left lung were 13.6 and 13.4 per cent, and the mean medial surface areas per square centimeter of lung tissue in right and left lung were 388 and 309. Among cases of comparable age in our series of normal lungs[5] the mean medial thickness was 7.7 per cent and the mean medial surface area 132. This shows that in DuShane and associates' case there was marked medial hypertrophy, roughly equal in the two lungs. The finding is in agreement with the expectation of pulmonary arterial medial hypertrophy when the pulmonary circulation is in open communication with the aorta and the pulmonary arterial pressure is at systemic level.

Summary

A case is reported of a 20-day-old infant with origin of the right pulmonary artery from the ascending aorta. Besides its abnormal origin, the artery was stenotic in its proximal half. We believe the malformation results from persistence of the distal (instead of the proximal) part of the primitive sixth aortic arch and of a portion of the right dorsal aorta. The presence of ductal tissue in the wall of the right pulmonary artery supports this concept.

The pulmonary vasculature in the two lungs showed great differences in medial and intimal characteristics. A second case of origin of the right pulmonary artery from the aorta, de-

scribed elsewhere, provided material for comparative study of the structure of the right main pulmonary arteries and the intrapulmonary branches.

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If therefore some may be apt to think that I have sometimes too far indulged conjecture, in the inferences I have drawn from the events of some experiments; they ought to consider that it is from these kind of conjectures that fresh discoveries first take their rise; for though some of them may prove false, yet they often lead to further and new discoveries. It is by the like conjectures that I have been led on step by step, through this long and laborious series of experiments; in any of which I did not certainly know what the event would be, till I had made the trial, which trial often led on to more conjectures, and farther experiments.—STEPHEN HALES, B.D., F.R.S. *Haemastatics.* Preface, Vol. II, London, 1733.

Cor Triloculare Biatriatum

Survival to Adult Life

By WILLIAM N. CHAMBERS, M.D., MODESTINO G. CRISCITIELLO, M.D., AND FAIRFIELD GOODALE, M.D.

A HEART comprised of atria and a single ventricle, cor triloculare biatriatum, represents an unusual congenital defect. In her atlas Abbott[1] described this as the unique defect in only 13 of 1,000 malformed hearts. Fourteen other hearts in her series had some anomaly in addition to a single ventricle. To date almost 100 patients with this defect have been reported in the medical literature but of these only 14 have reached adult life. Our patient is the fifteenth adult with cor triloculare biatriatum to be reported.

Case Report

A 41-year-old woman with cyanotic congenital heart disease was observed at the Hitchcock Clinic and Hospital at intervals for 10 years preceding her death. She had also been seen at various centers in Boston and New York. She had been cyanotic from birth, and a diagnosis of congenital heart disease was made at 2 years of age. Save for influenza at 2 and scarlet fever at 6 years, she had no unusual childhood diseases. Her growth and development were normal. Her activities were moderately restricted by dyspnea and easy fatigability. On graduation from high school she became a medical records' librarian. In 1936, she married an engineer but was divorced within a year. In 1940, 17 years before her death, she had the first of many episodes of hemoptysis. At that time the dyspnea, which had never been severe, gradually increased, though it did not incapacitate her. Despite this and a tempestuous domestic and emotional life, she continued to work effectively until 2 years before her death.

The first attempt to establish the type of anomaly was made in 1944. The following defects were suspected: atrial septal defect, persistent right aortic arch, subaortic stenosis, and right ventricular hypertrophy.

Physical examination in 1947 showed deep cyanosis and marked clubbing of the fingers and toes. The blood pressure was 120/70. The retinal vessels appeared dilated and full. The chest was normal. The heart was not enlarged to percussion. Rhythm was regular and the rate was 100 per minute. P_2 was accentuated but not split and was greater than A_2. M_1 was greater than M_2. A grade-II blowing systolic murmur was loudest in the second left interspace. The lungs were clear to percussion and auscultation, and the liver and spleen were not palpable.

The hematocrit value was 75 and the hemoglobin was 21.3 Gm. per cent. The white blood cells were normal, and the platelets were not increased. The sedimentation rate was normal. Urinalysis was negative.

On fluoroscopy the heart was not enlarged but there was slight fullness of the right ventricular shadow. The main pulmonary artery did not appear enlarged but there was engorgement of the right pulmonary artery and to a lesser degree of the left. Engorgement extended well into the smaller vessels of each lung. There was no hilar dance and no atrial enlargement. The aorta appeared normal. Pulsations were of normal amplitude (fig. 1). The electrocardiogram was consistent with atrial hypertrophy. No specific pattern of ventricular hypertrophy could be determined, though some abnormality of intraventricular conduction was suspected (fig. 2). A tentative diagnosis of Eisenmenger's complex with secondary polycythemia was made. Cardiac catheterization and angiocardiography were refused by the patient at that time.

In June 1954, she again noticed increasing dyspnea and had several bouts of hemoptysis. Her family physician therefore performed a phlebotomy and removed between 150 and 200 ml. of blood without incident. The following week during a second phlebotomy, after approximately 100 ml. had been removed, the patient suddenly felt dizzy and faint and complained of numbness of the roof of her mouth. The procedure was stopped. She then experienced increasing dizziness, weakness, and headache and became more cyanotic than previously. The patient reported sudden weakness of the left arm and leg. The increased cyanosis persisted for a week. The left-sided weakness gradually improved.

In October 1954, cardiac catheterization was performed at Mount Sinai Hospital in New York City (table 1).

These determinations showed that the oxygen

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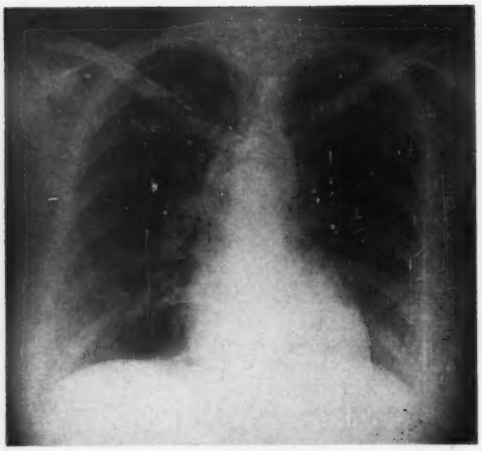

Figure 1A
X-ray of chest, posteroanterior view.

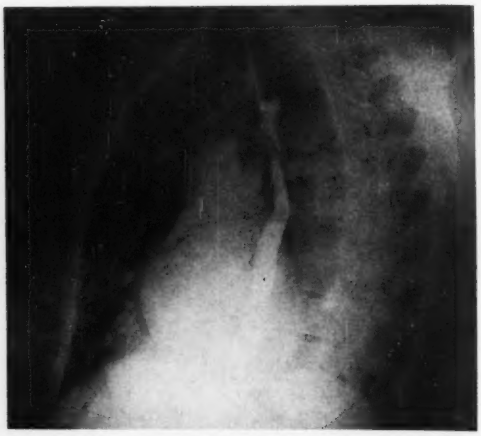

Figure 1B
X-ray of chest, left anterior oblique view with barium swallow.

content of the blood rose sharply from the right atrium to the ventricle. The oxygen content of the aorta, however, remained the same as the ventricular samples, indicating complete mixture of ventricular blood. It was concluded that the patient probably had a single ventricle. The possibility of pulmonary stenosis was considered, and angiocardiography was recommended but the patient refused. Surgical intervention was not advised.

Anticoagulants to combat the probable thrombotic episodes and radioactive phosphorus, to decrease the polycythemia, were considered inadvisable. Phlebotomies were thought contraindicated at the time in view of the neurologic complications following one of these procedures. The importance of adequate hydration was recognized.

In the spring of 1955 she became unable to work and was dyspneic on mild exertion. The syncopal episodes, vertigo, and hemoptyses persisted and signs of left hemiparesis were noted. The hematocrit value was 75, the hemoglobin was 20.4 Gm. per cent, and the red cell count was 8,650,000.

In October 1956 the syncopal episodes increased in severity and frequency. They were usually precipitated by physical exertion and emotional stress or fatigue, and were more frequent before menses. On hospitalization 3 months later physical examination showed little change. The heart size and the murmurs were the same. Marked secondary polycythemia persisted. Cardiac fluoroscopy showed prominence of the right ventricle and the right pulmonary artery, though not of the main pulmonary trunk. There were large peripheral divisions in the right lower lung fields. There was displacement of the esophagus posteriorly and to the right, which was thought to be due to a combination of aorta and large pulmonary artery. The lung fields, save for heavy vascular markings particularly on the right, were clear. The electrocardiogram showed no change.

Because of the rapid progression of symptoms and the severe polycythemia, the question of phlebotomy was again reviewed in great detail. Because it was considered essential to reduce the blood viscosity within a short time, it was decided to do phlebotomies, despite the risk and the patient's fear of them.

During the next 8 days 4 phlebotomies of 250 ml. were done cautiously with replacement of the same volume of saline solution. During the second phlebotomy the patient experienced numbness and tingling of the roof of the mouth with thickness of speech. She was subsequently noted to be more short of breath and more deeply cyanotic. On the tenth day, during a fifth phlebotomy she again complained of dry mouth and numb tongue after 75 ml. of blood had been removed. Aphasia, profound cyanosis, increased left-sided weakness, and slurred speech were followed by coma and repeated convulsions that cleared after intramuscular magnesium sulfate. No subsequent seizures occurred, but the speech remained thick and the signs of left hemiparesis persisted.

Her subsequent course was marked by recurring thrombotic episodes involving the brain as well as the left subclavian artery. Her condition deteriorated rapidly. Oral and intravenous fluids were increased to 4,000 ml. in an attempt to expand the plasma volume. No signs of congestive heart failure appeared, the urinary output was satisfactory, and there was gradual improvement with slow

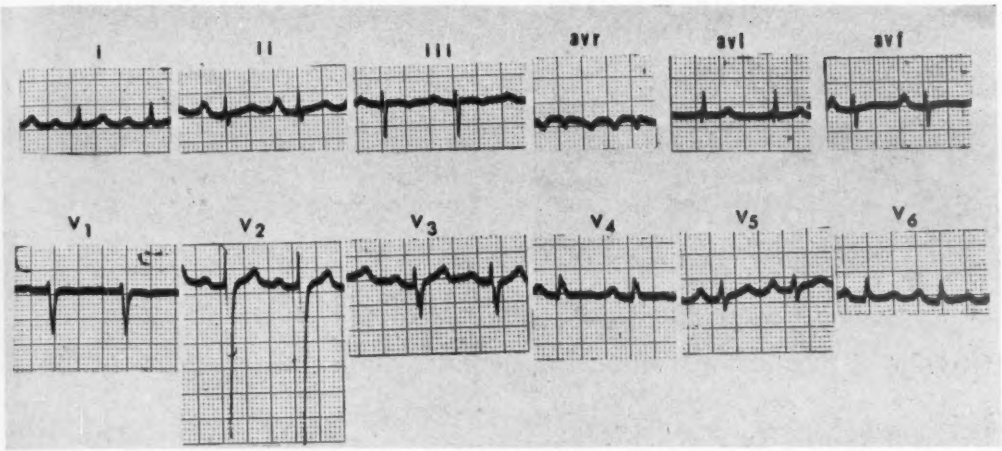

Figure 2

Electrocardiogram.

regression of the neurologic signs. The hematocrit value gradually dropped to 65 and persisted at this level. A left greater saphenous phlebitis, extending from the foot to the upper thigh developed. There were no signs of deep phlebitis, and no further thromboses were noted. Several days later she suddenly became comatose and died.

Autopsy Examination

The heart weighed 324 Gm. and was trilocular, composed of 2 atria, with an intact septum, and a single ventricle. Both venae cavae emptied normally into the right atrium, which was dilated to 2½ times normal size but contained no thrombi. It communicated with the common ventricle through a bicuspid valve 10 cm. in diameter. Dorsally, between the two leaflets, a puckered area of endocardium 1 cm. long appeared to be a rudimentary third leaflet. The great vessels leaving the heart were transposed (figs. 3 and 4). Neither the left atrium nor the pulmonary veins from the left lung, which entered it normally, were dilated. From the right lung a single dilated pulmonary vein, 2.5 cm. in diameter, emptied into the left atrium. Communication of the common ventricle with the left atrium was through a normal bicuspid mitral valve, 2.8 cm. in diameter. The aortic valve was normal, save for several small (0.6 by 0.4 cm.) firm, gray-yellow thrombi on each corpus Arantii. The coronary ostia and vessels were normal. The entrance to the pulmonary valve was small, measuring 1.6 cm. in diameter (fig. 5), and there was no differentiation of the valve into cusps. It was markedly stenotic with only a pinpoint lumen. Perched on its superior surface was a cone-shaped thrombus, 0.8 cm. in diameter, which was red-gray, firm, and granular

Table 1

Cardiac Catheterization

Site	O content (vols. %)	%O saturation	Pressures (mm. Hg)
Superior vena cava	13.6	48	6 mean
Inferior vena cava	16.4	57	8 mean
Right atrium (high)	14.8	52	6 mean
Ventricle (mid)	22.6	80	...
Ventricle (outflow)	19.8	70	112/5
Aorta	20.4	72	111/70, 87
Right brachial artery	20.5	72	111/69, 87
Right femoral artery	20.6	73	...
Aorta	20.5	72	94/68, 76
Capacity	28.8		

with a minute aperture less than 1 mm. in diameter at its tip. When explored with a probe this aperture was found to be continuous with the opening in the valve itself (fig. 6). Immediately distal to the stenotic pulmonary valve the main pulmonary artery was dilated to 6.9 cm. in circumference. The right division was markedly dilated to 4.0 cm. in diameter at its origin. The left measured only 12 cm. in diameter. Neither the pulmonary artery nor its branches showed atherosclerosis or thrombosis.

The ligamentum arteriosum was a fibrous cord. The innominate artery and the left subclavian artery arose normally but the lumen of the latter was occluded at its origin for 2.5 cm. distally by a firm, red-brown adherent thrombus. The left internal and external carotid arteries took separate origin from the aortic arch. The bronchial arteries were not followed. Microscopically the myocardium was normal.

The lungs together weighed 1150 Gm. At the

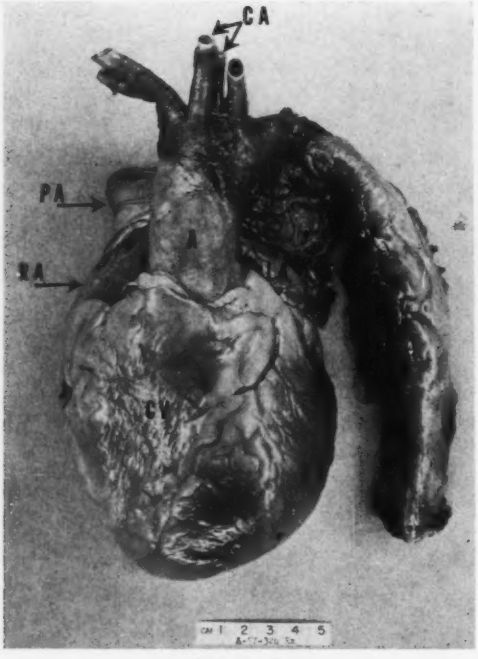

Figure 3

View of anterior surface of the heart showing the common ventricle (CV), and the right and left atria (RA, LA). The transposition of the great vessels is evident with the anteriorly placed aorta (A) and behind it the pulmonary artery (PA). The left internal and external carotid arteries (CA) take separate origin from the aortic arch.

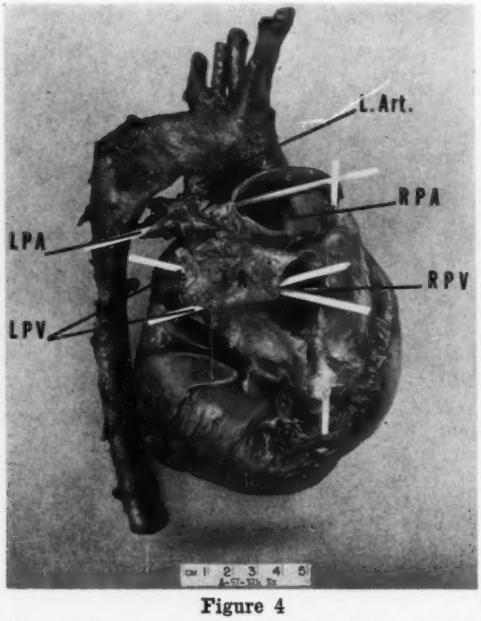

Figure 4

View of the posterior surface of the heart showing superiorly the markedly dilated right main division of the pulmonary artery (RPA), and its small left branch (LPA); below is the normal sized left atrium (LA) with the 2 left pulmonary veins (LPV) entering in the usual fashion while on the right is the single dilated pulmonary vein (RPV). The vertical stick indicates the ostia of the vena cava. The ligamentum arteriosum (L. Art.) is now a fibrous cord.

hilus of the right lung were two large vascular channels; the dilated right pulmonary artery and vein, the latter 5.0 cm. in diameter (fig. 7). No thrombosis was seen. The bronchi were normal. Microscopically all lobes showed extreme dilatation of bronchial and pulmonary arterioles and alveolar capillaries. This appearance was so striking in places as to give the tissue a "honeycombed" appearance (fig. 8*A*). There was no medial hypertrophy in bronchial or pulmonary arterioles of any size, but the latter showed slight to moderate fibrous intimal thickening. Many bronchial and pulmonary arterioles contained recanalized thrombi or emboli (fig. 8*B*). Definite anastomoses between bronchial and pulmonary arterioles were present (figs. 8*C* and 8*D*). One small recent infarction was present in the right upper lobe. There was no pneumonia.

The spleen contained a small healing infarction.

Areas of softening, degeneration, and cyst formation were found grossly in the right side of the brain.

Microscopically the bone marrow showed marked hyperplasia, which was predominantly in the red cell series.

The main anatomic diagnoses were: Cor triloculare biatriatum with transposition of great vessels; pulmonary stenosis, congenital, with superimposed thrombosis; bicuspid "tricuspid" valve; single pulmonary vein, right; dilatation, moderate, main pulmonary artery and marked, right pulmonary artery; bronchopulmonary arteriolar anastomoses; emboli, recanalized, multiple, bronchial and pulmonary arterioles; thrombosis, organizing, of proximal left subclavian artery; infarcts of cerebrum and pons, spleen, and lung.

Discussion

Even with the sophisticated technics available today, an accurate premortem diagnosis of cor triloculare biatriatum is unusual. There is no uniform pattern,[2] but variation is considerable in the degree of cyanosis, in the characteristics of the murmurs, in the appearance of the electrocardiogram,[3] and in the

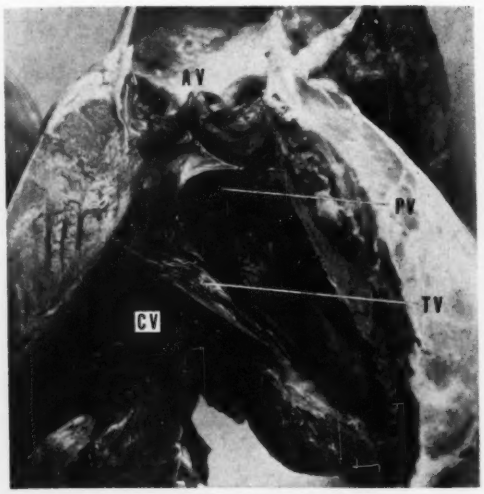

Figure 5

The heart opened anteriorly shows the thick-walled common ventricle (CV), the aortic valve above (AV), and just below it the small entrance to the pulmonary valve (PV). Still more inferiorly the edge of the bicuspid "tricuspid" valve (TV) is visible. Small thrombi are present on the aortic valve cusps.

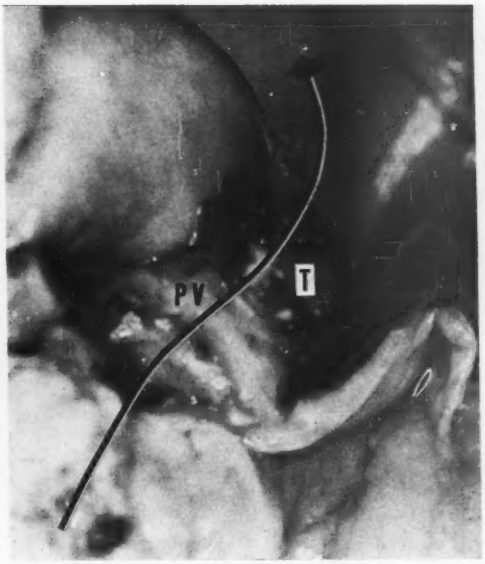

Figure 6

An anterior view of the unopened, cone-shaped and markedly stenotic pulmonary valve (PV) shows the firmly adherent thrombus (T) on top of it. The arrow indicates the direction of blood flow through the pinpoint lumen on the superior surface of the thrombus.

contours of the heart at fluoroscopy. A systolic murmur has been recorded in all cases, but its position has varied from apex to second left interspace. Despite the absence of septal tissue very few of these patients show bundle-branch block or intraventricular conduction defects. Cardiac fluoroscopy often reveals evidence of increased pulmonary blood flow, but there is no characteristic x-ray configuration of the heart shadow or of the great vessels. Those defects presenting most confusion in differential diagnosis are Fallot's tetralogy and the Eisenmenger pattern. The accurate diagnosis of a single ventricle rests upon both angiocardiography and cardiac catheterization. The simultaneous filling of the aorta and pulmonary artery from a common ventricular chamber, as seen on the angiocardiogram, indicates the presence of a single ventricle; the demonstration of identical oxygen contents in the pulmonary artery, the aorta, and the ventricle, confirms the diagnosis.

With rare exceptions a single ventricle is associated with transposition of the great vessels, so that the aorta lies anterior to the pulmonary artery. Often a rudimentary outflow chamber, or persistent bulbus cordis can be recognized, and an anatomic classification has been devised by Rogers and Edwards[4] relating the position of the aorta and pulmonary artery to this outflow chamber. Many hearts with a single ventricle have been found to have an additional anomaly. Among these have been patent ductus arteriosus,[5] subaortic stenosis,[6] atresia of the mitral valve and of the ascending aorta,[7] and atrial septal defect.[8]

As emphasized by Rogers and Edwards,[4] patients with cor triloculare biatriatum rarely live beyond childhood, and, indeed, 14 patients only have been recorded[1, 2, 8–13] who reached the age of 21 years or more. The oldest of these succumbed at the age of 56. Our patient who died at the age of 41 is the fourth oldest on record.

In relation to the problem of survival in patients with cor triloculare biatriatum, it is

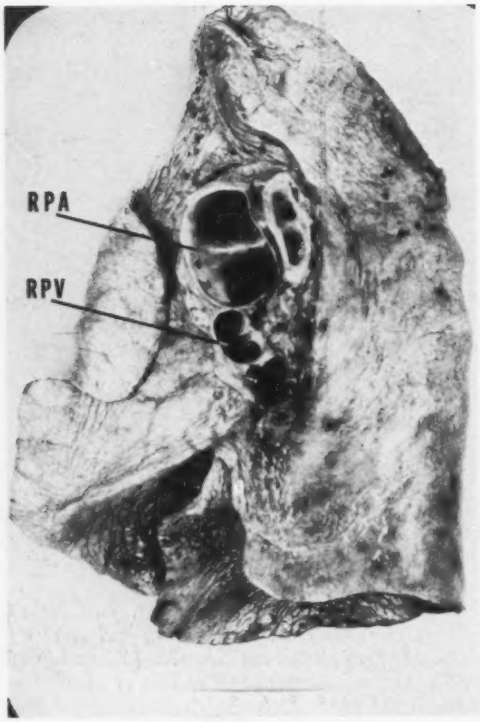

Figure 7

At the hilum of the right lung superiorly is the dilated right pulmonary artery (RPA) and below the dilated right pulmonary vein (RPV).

pertinent to review the physiology of one of those animal forms that normally possess only a single ventricle. Why is it, for example, that the frog with its single ventricle does so well when man, with his, does so poorly? The immediate answer is that the frog has other means of separating the pulmonary from the systemic distribution of blood. The frog[14] has only a single large vessel, the truncus arteriosus, arising from its single ventricle (fig. 9). This trunk divides into 2 main branches, each of which immediately subdivides into 3 major arteries. One, the pulmocutaneous artery, carries blood to the organs of respiration, the lung, and the skin. The systemic artery carries blood to the extremities and to the abdominal viscera, and the carotid artery carries blood to the head. The so-called carotid gland, a network of small vascular channels, is interposed in the course of the carotid artery, acting as a segment of high resistance. The truncus arteriosus (fig. 10) at a point beyond the semilunar valves, is divided by a long tongue of tissue, attached along most of its dorsal edge, but free ventrally. This is the longitudinal or spiral valve. The mouth of the truncus is near the right atrioventricular valve, so that blood coming from the right atrium, lowest in oxygen content, is the first to be delivered into the truncus at the onset of ventricular systole. The resistance in the pulmocutaneous circuit is lowest, so that this initial volume of unsaturated blood flows into the organs of gas exchange. As the ventricle approaches midsystole, muscle tissue in the wall of the truncus itself contracts, narrowing this channel and forcing the free end of the spiral valve to close over the orifices of the pulmocutaneous arteries. During the midportion of systole, blood flows into the systemic artery where the next lower level of resistance exists. Finally, as the systemic system is filled and systolic pressure reaches its peak, the resistance of the carotid gland in the carotid artery is overcome, and the last volume of blood, chiefly that which has flowed from the left atrium into the left side of the ventricle, with its higher oxygen content, now moves to the head. The thick wall of the frog ventricle contains many little pits or recesses, and acting like a sponge, absorbs much of the blood as it enters from the atria on either side, reducing the degree of admixture that otherwise might occur in the free cavity.

In man, possessing no spiral valve, no carotid gland, and no myocardial sponge, there must be some other mechanism to permit survival. A review of the case histories of long-term survivors failed to reveal the uniform presence of any single associated anomaly. In searching among these for cases similar to our own, we found only a single report in which a deformity of the pulmonary valve accompanied the single ventricle. Carns et al.[9] described a 44-year-old woman who had a rigid, bicuspid pulmonary valve with poststenotic dilatation of the pulmonary artery. This patient, severely cyanotic, with a red blood count of 8.4 million, died after having developed thrombophlebitis of the right sub-

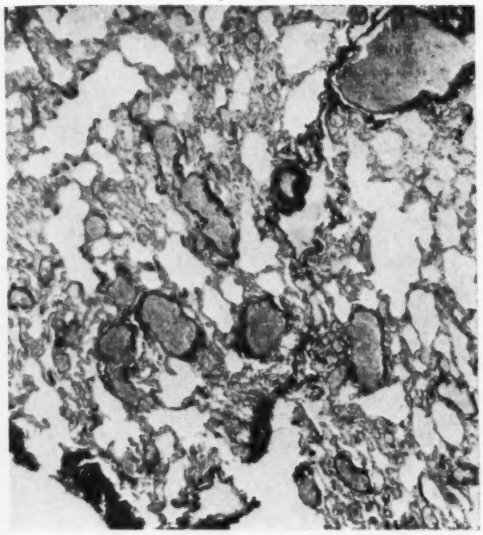

Figure 8A

A representative view of the thin-walled and markedly dilated blood vessels of the lung parenchyma derived from both pulmonary and bronchial arteries.

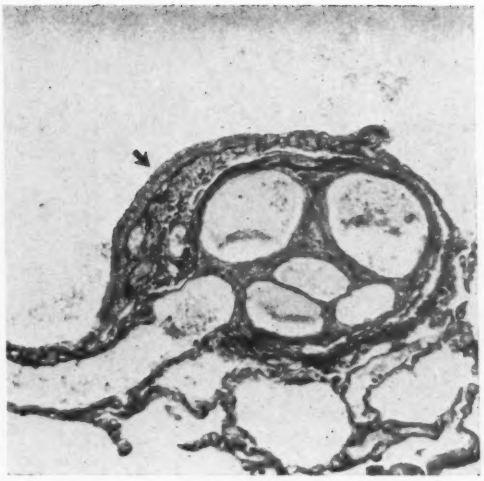

Figure 8B

A dilated bronchial artery containing a recanalized thrombus. The lining of the bronchus is indicated by the arrow.

clavian vein. A patient reported by Mehta and Hewlett[8] lived until the age of 56, but had a persistent truncus arteriosus. The pathway of her pulmonary blood flow was not recorded. One young man[5] who died at 18 years of a ruptured pulmonary artery was found to have a hypoplastic aorta and a patent ductus arteriosus. At least in terms of gross morphology, there is no consistent pattern among this older-age group. Clinically, the only common denominator has been a fairly severe degree of cyanosis. The only exception is Herndon's case,[12] a 49-year-old man in whom cyanosis was not prominent.

Unfortunately almost none of the reports of these cases includes a description of the microscopic appearance of the lung and its vasculature, for it is very likely that changes in the intrapulmonary vascular network of these patients are of paramount importance in their survival.[6] In the presence of a single ventricle, the distribution of blood flow between the aorta and the pulmonary artery is determined by the resistance in each circuit. Because of its easy distensibility, the pulmonary vascular tree ordinarily presents much the lesser resistance, and as is the case in most patients with this anomaly, the greater volume of blood flows to the lungs. Although oxygenation of this larger volume of blood may contribute to a higher net saturation of the blood mixed in the single ventricle, the obvious disadvantage is that systemic blood flow may be critically low. This deficit in systemic flow accounts for the meager development and early death of most infants born with a single ventricle.

The introduction of some obstruction to flow in the pulmonary circuit, either at the level of the pulmonary valve or in the small pulmonary arteries, would tend to balance the distribution of blood, so that a more adequate volume could be directed out the aorta. This increase in pulmonary resistance can be produced by vasoconstriction or by structural changes in the pulmonary arteries. The resultant shift of blood away from the pulmonary circuit, as it were, would result in a lower level of saturation of mixed ventricular blood. Hence a more satisfactory systemic flow would be gained at the price of more cyanosis. It is possible, of course, that such pulmonary vascular obstruction would become progressively more severe as the result of medial hypertrophy, intimal proliferation, or mul-

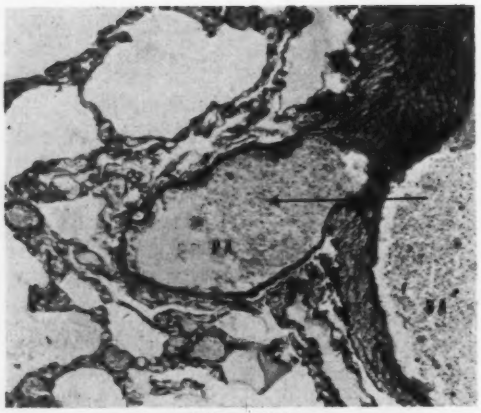

Figure 8C

A thin-walled pulmonary arteriole (PA) communicates with a thick-walled bronchial artery (BA). Serial sections show the communication to be complete. An arrow indicates the probable direction of blood flow.

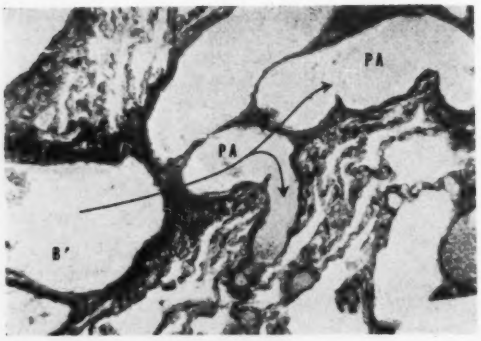

Figure 8D

A markedly dilated bronchial artery (BA) communicates with equally dilated pulmonary arterioles (PA). The edge of the bronchus is in the upper left corner. An arrow indicates the probable direction of blood flow.

tiple intravascular thromboses. However, under such circumstances, the development of anastomotic channels between branches of bronchial and pulmonary arteries would provide an avenue for continued adequate flow of blood past alveolar spaces. This appeared to have been the case in our patient as well as in one reported by Heath.[2]

A patient can survive to adult life if he can walk this knife edge between a critically reduced systemic output (when pulmonary resistance is too low) and a critically reduced oxygen uptake (when pulmonary resistance is too high). Our patient, with a severe degree of pulmonary valvular stenosis but with multiple bronchial-pulmonary arteriolar anastomoses, was apparently able to accomplish this balance. It is pertinent here to refer to the case report of a boy[15] who, with the mistaken diagnosis of Fallot's tetralogy, underwent surgical correction of pulmonic stenosis. He died 3 hours after a successful valvuloplasty and was discovered to have had a single ventricle rather than the tetralogy pattern. Release of his pulmonary obstruction may very well have been his undoing.

In her later years our patient appears to have sustained multiple pulmonary emboli or thromboses with further increase in the pulmonary resistance and further reduction in oxygen uptake. The increasing erythemia compensated to some extent perhaps, but the attendant increase in blood viscosity brought with it the hazard of cerebral vascular thromboses.

A real dilemma of therapy and management was posed by our patient. On the one hand, her condition was deteriorating and she had already suffered cerebral damage from previous thromboses. The high incidence of thromboembolic phenomena under such circumstances was recognized, and reduction of the blood viscosity was urgently needed. On the other hand, we were aware of the known, though unpublished, high incidence of thromboses in patients with congenital heart disease and polycythemia following phlebotomy. After careful consideration phlebotomies were cautiously performed with the disastrous results reported.

A total of 7 phlebotomies was done. Three of these were followed either immediately or within 24 hours by evidence of cerebral damage. The final phlebotomy appears to have initiated a period of prolonged coma and convulsions, with both left and right hemiplegias. Several observers have stated that experience in patients with congenital heart disease and secondary polycythemia has led them to abandon phlebotomy as a means of lowering the

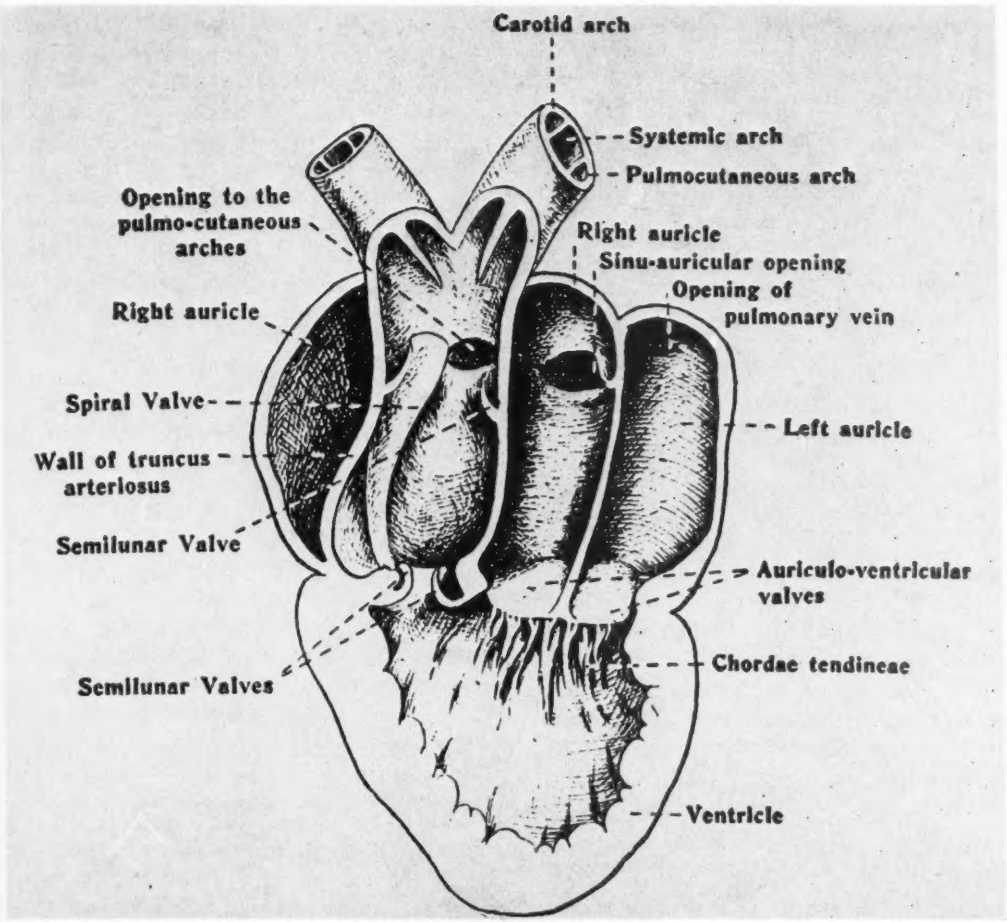

Figure 9

Frog heart.

hematocrit level.[16–18] Repeated instances of acute neurologic changes, some of them transient, others permanent, have been observed. Sudden death has occurred during or immediately following this procedure. As in our case, the amount of blood withdrawn is not always a factor, since this adverse effect has been noted with as little as 75 to 100 ml. No specific reference to this complication of phlebotomy was found in medical literature.

The mechanism for the occurrence of thrombotic episodes during phlebotomy in patients with congenital heart disease and secondary polycythemia is not understood. There are a number of possible contributing factors that must be considered.

In secondary polycythemia the oxygen saturation of the arterial blood is reduced. This suggests that polycythemia is secondary to hypoxemia. Polycythemia with increased hemoglobin content is a consequence of arterial unsaturation.[19] The increased oxygen-carrying capacity achieved in this way is an extremely useful compensatory mechanism until the polycythemia reaches the hematocrit value of 80 or more. At these levels the benefits derived from the increase in available oxygen are outweighed by the disadvantages

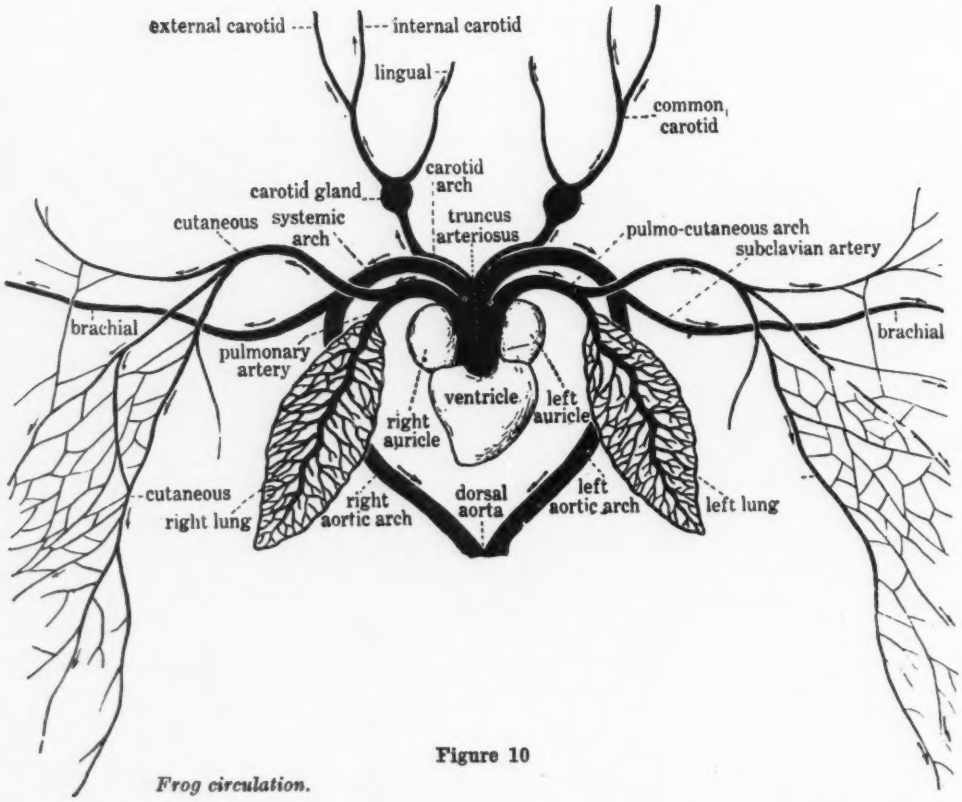

Figure 10

Frog circulation.

of high blood viscosity. Rudolph, Nadas, and Borges[20] have shown that when the hematocrit value reaches 65 to 70, further increase entails a considerable rise in blood viscosity resulting in an impediment to blood flow, sludging, and even decreased delivery of oxygen to the tissues. The relationship is in the form of a hyperbolic curve. At lower hematocrit levels a fairly large rise in the hematocrit value is required to produce significant change in viscosity. At higher hematocrit levels, however, only minor increases of the hematocrit value produce marked increases in viscosity.[21]

Multiple thromboembolic phenomena are typical of the late course of patients with well compensated cyanotic congenital heart disease. This patient was in the early menopause and was approaching the age of degenerative vascular disease, which increases the likelihood of thromboembolic phenomena.

Tyler and Clark[22,23] reported that paroxysmal loss of consciousness or convolutions occurred in approximately 18 per cent of a series of 336 patients with congenital heart disease. Those forms of congenital heart disease that had the highest incidence of loss of consciousness, or convulsions, also were marked by lower systemic arterial oxygen content and oxyhemoglobin saturation. The attacks were most frequently seen in patients whose cardiac defect provided a physiologic potentiality for large and rapid variations in the amount of venous blood reaching the systemic circulation.

Thromboses in relation to periods of stress have been shown to occur with marked reduction in clotting time. Increase in viscosity occurs during painful experience, vigorous effort, and in periods of alarm or anxiety. In

the studies by Schneider[24] it has been shown that when people were subjected to interviews arousing personal conflicts and conscious or unconscious anxiety, there occurred in association with elevation of arterial blood pressure shortening of the clotting time and sedimentation rate, and an increase in the blood viscosity with rise in the hematocrit value.[24]

It is likely that all these factors played a part in this patient's adverse response to phlebotomy.

Summary

The case of a 41-year-old woman with congenital pulmonary stenosis and single ventricle is reported. This is the fifteenth instance recorded of survival to adult life of a patient with cor triloculare biatriatum. Increased pulmonary resistance may be a reason for her comparative longevity, and the significance of prominent bronchopulmonary anastomoses has been discussed. This patient's course demonstrates the hazards of phlebotomy in congenital heart disease and secondary polycythemia. The mechanism for this adverse effect is not understood and warrants further study. Although others have discussed the problem informally, this appears to be the first documented report of the precipitation of multiple cerebral thromboses following phlebotomies.

Acknowledgment

We are indebted to Drs. W. B. Castle, W. T. Goodale, A. Grishman, O. J. Marcil, and M. Raisbeck, for their cooperation in supplying records and observations on this patient.

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SYMPOSIUM ON CORONARY HEART DISEASE

Measurements of Enzymes in the Diagnosis of Acute Myocardial Infarction

By MILTON W. HAMOLSKY, M.D., AND NATHAN O. KAPLAN, PH.D.

A SIGNIFICANT recent advance in the diagnosis of heart disease has resulted from the development and widespread application of methods to quantitate levels of enzyme activities in the blood or serum of man. From the practical clinical standpoint, the major enzyme systems of present value in this regard are the transaminases (glutamic-oxalacetic and glutamic-pyruvic transaminase) and lactic dehydrogenase. An increase in the serum level of activity of these enzymes, in the appropriate clinical setting, has proved to be a valuable laboratory indicator of myocardial damage. It would not be practicable to discuss extensively the large and rapidly expanding pertinent literature; furthermore, detailed reviews of various aspects of this subject are available.[1-5] This communication, therefore, will attempt to summarize certain aspects of (1) the biochemical and experimental bases of the tests, (2) development of methodology, (3) clinicopathologic correlations with the laboratory results, and (4) a critique of their sensitivity, specificity, diagnostic and prognostic accuracy, advantages, and limitations.

Transaminases

Biochemical Background

The term "transaminase" (also called "aminopherase") refers to a group of enzyme systems that catalyze the intermolecular transfer of an amino group (NH_2) from a donor α-amino acid to an acceptor α-keto acid —viz.

$$\underset{(\alpha\text{-amino acid})}{\overset{\text{R}}{\overset{|}{\text{NH}_2\text{-CH}\cdot\text{COOH}}}} + \underset{(\alpha\text{-keto acid})}{\overset{\text{R}'}{\overset{|}{\text{O}=\text{C}\cdot\text{COOH}}}} \rightleftharpoons \overset{\text{R}}{\overset{|}{\text{O}=\text{C}\cdot\text{COOH}}} + \overset{\text{R}'}{\overset{|}{\text{NH}_2\cdot\text{CH}\cdot\text{COOH}}}$$

Such a transamination had been demonstrated in model, nonenzymatic reactions. Braunstein and Kritzmann[6] first demonstrated the presence of enzymes catalyzing such reactions in pigeon breast and rabbit muscle. Subsequent studies have revealed that transamination is probably the most important metabolic mechanism in both the formation and deamination of many amino acids in various tissues. There are two separable major transaminating enzymes in heart muscle:

A. The glutamic-oxalacetic transaminase (GOT), which catalyzes the reaction

l-Glutamic acid + oxalacetic acid $\rightleftharpoons$ α-ketoglutaric acid + l-aspartic acid

and B. The glutamic-pyruvic transaminase (GPT), catalyzing the reaction

l-Glutamic acid + pyruvic acid $\rightleftharpoons$ α-ketoglutaric acid + l-alanine.

These two systems are widespread in higher plants, many microorganisms, and in the blood and tissues of animals (in man, in the following descending order of concentration: heart muscle, skeletal muscle, brain, liver, kidney, testis, lung, and spleen). Pyridoxal phosphate (vitamin B_6 derivative) is the fundamental coenzyme for this reaction. It is

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This article constitutes, in part (Dr. Kaplan), publication no. 63 of the Graduate Department of Biochemistry at Brandeis University, Waltham, Massachusetts.

postulated that the pyridoxal phosphate first reacts with the amino acid to form a keto-acid and pyridoxamine phosphate, which then donates the amino group to another keto-acid, thus effecting the ultimate transamination. In consonance with this view, B_6 deficiency results in lowered levels of transaminase activity.

Methods of Measurement

It is essential to note that, at the present stage of development, the available methods of enzymology measure rates of reactions, i.e., they reflect over-all levels of activity and not the actual concentration of a specific enzyme molecule. The manifold complexities of serum with its possible inhibitors, precursors, activators, complex formation, etc., necessitate this mental reservation and remind us of the completely empirical status of current methods. Furthermore, some confusion has resulted from the early multiplicity of methods with the resultant differences in "normal" and "abnormal" values, necessitating critical evaluation of the specific methods employed in the reporting laboratory.

GOT and GPT are the two major transaminases of clinical import. When their activities are measured in serum, the appropriate terms in current usage are SGOT and SGPT (serum glutamic-oxalacetic and serum glutamic-pyruvic transaminase, respectively). Various methods of measurement have been employed.[4]

1. *Chromatography:* Under standardized conditions, aspartate or alanine is incubated with α-ketoglutarate and the enzyme source, and the resultant glutamate is measured by quantitative paper chromatography.

2. *Fluorometry:* Direct measurement by fluorometry is not possible. Instead, advantage is taken of the ingenious enzymologic technic of "coupling" wherein the product of one enzymatic reaction serves as a reactant in a more easily measured second reaction. Measurement of the rate of the second reaction serves to quantitate indirectly the rate of the first reaction. Thus, the glutamic-oxalacetic transamination reaction is coupled to a second reaction in which the oxalacetate serves to oxidize reduced diphosphopyridine nucleotide (DPNH) to DPN in the presence of an excess of malic dehydrogenase. The DPN is measured by fluorescence of its condensation complex with methyl-ethyl ketone. The rate of DPN formation thus serves to quantitate the rate of the first reaction.

Reaction 1—Aspartate + α-ketoglutarate $\underset{\text{transaminase}}{\rightleftharpoons}$ oxalacetate + glutamate

Reaction 2—Oxalacetate + DPNH $\underset{\text{dehydrogenase}}{\overset{\text{malic}}{\rightleftharpoons}}$ malate + DPN

Similarly, for SGPT, the pyruvate formed in the first step oxidizes DPNH to DPN in the presence of lactic dehydrogenase and the rate of DPN formation serves as a measure of the rate of the initial reaction.

3. *Colorimetry:* For SGOT activity, the oxalacetate is converted to pyruvate; for SGPT, pyruvate is formed directly. The intensity of the color reaction of pyruvate with dinitrophenylhydrazine then serves as a measure of the over-all reaction.

4. *Spectrophotometry:* Here again, the coupling reaction is used and the rate of formation of DPN (reflecting the transamination reaction) is measured by the rate of decrease in light absorption at 340 mμ, the absorption maximum for reduced DPNH.

Representative normal values for the different methods are presented in table 1.

Although such measurements have proved to be of distinct value in general clinical studies, certain theoretical objections have been raised. The technic of "coupling" the desired reaction with a second, dependent reaction introduces certain complexities of indirect measurement. Furthermore, nonlinear kinetics have been demonstrated in the coupled SGOT system. It has been reported that available preparations of malic dehydrogenase, the enzyme introduced to "make" the second reaction go, may themselves be contaminated with variable amounts of GOT. Finally, direct comparison of two or more different

Table 1

Representative Normal Values for Serum Transaminase Activities in Man[4]

Activity	Method	Normal values		
		Units	Range	Mean
SGOT	Paper chromatography	μM glutamate/ml./hr.	0.41— 1.36	0.622 ± 0.191
	Fluorometry	μM oxalacetate/ml./hr.	—	1 ± 0.05
	Colorimetry	Colorimetric unit*	4 —40	16 ± 8.0
	Spectrophotometry	Unit/ml./min**	9 —40	20 ± 7
SGPT	Paper chromatography	μM glutamate/ml./hr.	0.21— 1.01	0.525 ± 0.146
	Fluorometry	μM pyruvate/ml./hr.	—	0.8 ± 0.5
	Colorimetry	Colorimetric unit*	1 —45	22 ± 12
	Spectrophotometry	Unit/ml./min.**	—	16 ± 9

*One colorimetric unit = the activity of 1.0 ml. of serum resulting in formation of chromogenic material equal to 1 μg. of pyruvate under standard conditions.

**One spectrophotometric unit = decrease in optical density at 340 mμ of 0.001 under standard conditions.

methods has revealed poor correlations in certain instances. Once again, we are reminded of the completely empirical status of present-day methods and of the need for critical clinical evaluation of the seemingly precise laboratory answer.

The method most widely used is based on the original, simpler spectrophotometric method of Karmen, Wroblewski, and La Due[7] and the generally accepted normal range has been 8 to 40 units. However, Rowell and Smith found, in 50 normal adults, SGOT activity of 19 ± 4.5 units and thus believe that values greater than 28 units are abnormal.[8] Similarly, for SGPT, an upper limit of normal of 21 units was based on findings in normal subjects of values of 12 ± 4.2 units. Their suggestion that previously reported "false negatives" may have been due to an erroneously high "normal" range underscores the need for further study and critical evaluation of this fundamental aspect of the problem.

Enzyme activity is strikingly constant in health, remaining essentially unaltered by ingestion of food, exercise, or storage at room temperature for 24 hours or at 0 to 5 C. for 2 weeks.

Clinicopathologic Correlations

Under normal conditions the abundant transaminases are confined, almost exclusively, within tissue cells and only very small amounts are found in the circulation. It is this relatively small "baseline" serum level which first suggested and has permitted ready detection of increased serum values resulting from destruction of tissue and the assumed release of enzyme from the large tissue stores. For example, dog heart tissue contains 300,000 units GOT per Gm. wet weight. It is not yet clear whether the increased serum levels, sometimes very large, are due wholly to the release of intracellular enzyme from necrosis of the myocardium, since it has been suggested that the increased amounts in serum are sometimes greater than the estimated stores of the entire myocardium. Alternative explanations then postulated, although not yet demonstrated, are a decrease in the body's degradative or excretory mechanisms or stimulation, by an unknown mechanism, of increased production or release of enzyme by other non-necrotic tissues.

There appears to be a highly effective mechanism, at present obscure, for the rapid elimination or degradation of the enzymes. Fleisher and Wakim[9] injected massive amounts of GOT intravenously into dogs, causing an increase in serum activity some 212 times the preinjection value. In 24 hours, 97 per cent of the enzyme activity had gone, and the control level was reached by the end of the third day.

La Due, Wroblewski, and Karmen[10] were the first to demonstrate that SGOT is increased above normal during the first few days after myocardial infarction in man—an observation that has been widely confirmed and extended. A significant rise has been detected within 6 to 12 hours of the estimated transmural infarction, generally reaching a peak some 2 to 15 times normal levels in 24

to 48 hours and returning to normal range by the fourth to seventh day. In certain cases, however, an elevation was not detected until 36 hours after the onset of symptoms and return to normal occurred as soon as 48 hours.

These clinical findings have been strongly supported by experimental studies of myocardial damage by several workers using various technics, revealing excellent correlations of increased serum levels of enzyme activity with tissue damage. Significant elevations of SGOT, although short-lived, have been found with experimentally induced infarcts of less than 1 Gm. of myocardium. There was a suggestive correlation between the size of the infarct and the height and duration of increased serum enzyme activity. Enzyme levels decreased rapidly in infarcted muscle as compared to normal muscle. In almost every instance, serum enzyme levels were not increased in the presence of significant myocardial ischemia without histologic necrosis. Similarly, experimental pulmonary infarction or pericarditis in dogs usually resulted in no increase in SGOT or SGPT.

In man, with the obvious limitations of precise definitions, a generally rough correlation of extent of damaged tissue and increase of enzyme activity has been suggested. Although a peak rise above 300 units has generally indicated a poor prognosis, frequent exceptions at both extremes (recovery in patients with extremely high levels, death in patients with only slight increases) render the actual level of little prognostic value in a given case.

SGPT is frequently normal in the face of elevated SGOT in the less extensive infarctions, but may rise in the presence of large infarcts. Although it has been stated that SGPT is not elevated until SGOT values of 150 to 200 units are reached, Rowell and Smith[8] found 14 episodes of elevation of SGPT with SGOT values below 150 units.

Critique

A large experience suggests that the determination of SGOT (and to a lesser extent SGPT) is an extremely valuable diagnostic tool. Elevated levels in a patient with the suggestive clinical picture of precordial pain and characteristic electrocardiographic changes are, of course, additional confirmatory evidence. Of perhaps greater value are rises in enzyme levels in a patient with a suggestive history whose electrocardiogram is atypical, or obscured by previous myocardial infarction, digitalis administration, bundle-branch block, or the Wolff-Parkinson-White syndrome. A secondary rise in a patient with recent myocardial infarction is an important indicator of extension of the necrotic process. In a recent review of the pertinent literature, Agress[1] concluded that 96 per cent of 1,255 cases of clinically proved myocardial infarction revealed elevated SGOT levels—a very impressive correlation. He suggested that the occasional reported case of elevated SGOT without apparent infarction could be attributed to undetected small areas of infarction. Failure of serum enzyme activity to rise in most cases (usually all but the most severe) of pulmonary embolism or infarction, pericarditis, rheumatic carditis, cardiac arrhythmias, status anginosus, coronary insufficiency, or occlusion without infarction serves as a most useful adjunct in differential diagnosis of chest pain syndromes. The need for caution, however, is underscored by the scattered reports of occasional elevations in such instances, and by less complete correlation reported in other series. For example, White[11] reported 12 instances of "false negatives" in 24 cases of myocardial infarction. A major consideration relates to the timing of the specimens for, as stated above, the elevation may occur early, reach a peak transiently within 24 to 48 hours, and return to normal levels by the second or third day, thus precluding confirmation in a patient seen first after this time period. In other instances, elevations may not occur until 36 hours after the onset of symptoms and may persist until the seventh day. Thus, serial determinations are necessary and various sampling schedules have been adopted, e.g., daily determination or one sample between 12 and 24 hours and a second one between 36 and 48 hours after the assumed clinical event.

The level of SGOT activity appears to be unaffected by the presence of several other

major disease processes,[1] such as heart failure, various infectious diseases, metabolic and endocrine diseases, arthritis, anemias, renal shutdown, venous hypertension, or by the administration of digitalis or quinidine. Activity levels do not correlate with various other factors such as age, sex, race, alterations in leukocyte count, sedimentation rate, body temperature, or urinary volume.

Recent studies have correlated very high levels of SGOT (>500 units) in cardiac patients with central hepatic necrosis attributed to hypotension, reduced cardiac output, and reduced flow[12] or acute right heart failure[13] with or without demonstrable myocardial necrosis.

It is pertinent to note other disease processes that may lead to elevated values although the clinical picture usually suffices to exclude them from serious consideration. Thus, transaminase levels are increased in virtually every type of liver disease (infectious, nutritional, obstructive, toxic, and neoplastic). In addition to the usually distinctive clinical features, differential diagnosis is aided by judicious use and interpretation of other liver function tests and by the usually greater elevation of SGPT values (in conjunction with the SGOT) in cases of liver-cell injury. Other pathologic states that may be associated with increased enzyme levels are: (1) intracardiac surgery, (2) administration of salicylates, opiates, or coumarin-type anticoagulants, (3) various forms of primary muscular and neuromuscular diseases (muscular dystrophy, muscular pseudohypertrophy, acute dermatomyositis, paroxysmal myoglobinuria, surgical trauma, gangrene of the toes), (4) acute pancreatitis, (5) extensive central nervous system damage as in massive cerebrovascular thromboses or hemorrhage, (6) toxemia of pregnancy, (7) hemolytic crises, (8) crush injuries or burns, and (9) infarction of kidney, spleen, or intestine.

Lactic Dehydrogenase

Biochemical Background and Methodology

Lactic dehydrogenase (LDH) refers to a group of enzymes that catalyze the reversible oxidation-reduction reaction between lactate and pyruvate, involving *pari passu* the conversion of the reduced and oxidized forms of the pyridine nucleotides (DPNH and DPN):

$$\text{Lactate} + \text{DPN}^+ \underset{}{\overset{\text{LDH}}{\rightleftharpoons}} \text{Pyruvate} + \text{DPNH} + \text{H}^+$$

This reaction is a critically important step in the carbohydrate metabolic cycle and, accordingly, the enzyme—a zinc-containing compound—is widespread, having been found in virtually every vertebrate and invertebrate species tested, in almost every mammalian tissue studied, and in many microorganisms. Recent exciting studies (see *Critique* below) have suggested a heterogeneity of the LDH enzyme moiety, not only in different species but also in different tissues within the same species, indeed within the same individual organism.

In the presence of the enzyme, lactate is oxidized to pyruvate ("forward reaction") while DPN is reduced to DPNH; conversely, the enzyme will also catalyze the "reverse reaction" in which pyruvate is reduced to lactate while the reduced DPNH is oxidized to DPN. Thus, measurement of enzyme activity can be carried out in either direction depending upon the initial substrates employed, proper conditions of pH, etc., and different clinics have adopted one or the other method. Snodgrass et al.,[5] in a detailed discussion of the respective merits, delineate their preference for the "forward" reaction (lactate $\longrightarrow$ pyruvate) on the basis of greater precision and convenience. Recent methodologic advances have culminated in the development of a relatively simple, "bedside" method of sufficient accuracy employing a commercially available photometer and prepared lyophilized reaction mixtures, requiring the addition only of the patient's serum. The basis of the quantitation is the direct spectrophotometric measurement of the rate of change of DPNH at its characteristic wave length of 340 mμ (increase in "forward" reaction, decrease in "reverse" reaction). A unit of LDH activity is defined as an increase in optical density units of 0.001 per minute per ml. of serum. A representative normal range is from 25 to 100 units at

23 C., averaging 59 units; thus a value greater than 100 units constitutes an abnormal elevation. As indicated above, however, different "normal ranges" have been established by various clinics using modifications of the basic technic. Thus, normal values have been published of 165 to 332 units per ml. of serum,[14] 90 to 100 units per 0.01 ml.,[11] 200 to 680 units per ml.,[3] or less than 270 micromols per 100 ml.[3] The serum may be obtained from fasting or nonfasting blood, and enzyme activity is essentially unchanged during storage at 4 C. for periods up to 10 days. Hemolyzed serum is unsatisfactory because of the high LDH content of erythrocytes.

Clinicopathologic Correlations

The high content of LDH activity in cardiac muscle and relatively low serum values again suggested the possible usefulness of study of serum levels in cases of myocardial damage. In the course of their sequential studies of the serum concentration of copper, then zinc, in various diseases, Wacker et al.[15, 16] found a marked increase of serum LDH activity in patients with acute myocardial infarction. This observation has been amply confirmed and extended and is the basis for the widespread use of this laboratory aid in diagnosis of myocardial disease. In characteristic cases of myocardial infarction, proved at autopsy, serum LDH activity was significantly increased above normal at some interval from 12 hours to 10 days after infarction in an extremely high percentage of cases—up to 100 per cent in certain series.[5] In general, enzyme activity was increased within the first 12 to 24 hours, rose to a peak in 3 to 4 days, gradually returning to normal by the eighth to fourteenth day. Thus, the optimal period of detection is from 2 to 6 days after infarction and the pattern of an abrupt rise in the first 3 to 4 days, followed by a gradual decline may itself serve as a strong indication of myocardial infarction. Increased levels occurred even in the absence of definitive electrocardiographic changes or consistent alterations in leukocyte count, sedimentation rate, etc. Elevated values in atypical or clinically unsuspected cases were confirmed by autopsy findings. Conversely, autopsy failed to reveal infarction in several cases dying with the diagnosis of acute myocardial infarction but in whom repeated LDH determinations were within normal limits. Several other reports indicate a very high correlation of elevated values in patients with an ultimate diagnosis of myocardial infarction, although not subjected to autopsy confirmation. In a study of other types of myocardial disease, increased values were found in some cases of severe congestive failure (usually with "congestive cirrhosis" of the liver) bacterial pericarditis, and severe digitalis intoxication; normal values were found in patients given coumarin anticoagulants or with heart block, prolonged arrhythmias, ventricular aneurysms, or subacute bacterial endocarditis. Elevated LDH values have been found in acute viral hepatitis, muscular dystrophy, leukemia, and certain cases of metastatic carcinoma.

Critique

Elevation of serum LDH activity is an extremely valuable indication of myocardial damage in appropriate cases. Although the question of sampling time must be considered in the failure to observe an increased LDH in suspected cases, repeated normal values are strong evidence against myocardial necrosis. It is pertinent to note that, although very high correlations have been observed in small series, the almost inevitable exceptions have been documented—normal values in patients with apparent myocardial infarction and elevated values in other disease states, without myocardial necrosis.

Such exceptions and the fact that, as with SGOT, elevated serum values are basically nonspecific, lend emphasis to recent basic investigations of the nature and mechanism of action of LDH. These studies have revealed findings of profound fundamental and potential clinical import, namely, the possibility that what is measured as over-all LDH activity of a given tissue or serum actually consists of several similar, yet actually different, molecular entities. Kaplan and his co-workers,[17] in a series of studies employing analogues of DPN and DPNH to measure catalytically

LDH activities of different tissues in several vertebrate and invertebrate species, in combination with electrophoretic and immunologic technics, have demonstrated striking differences in LDH of different species and, perhaps more pertinent to this discussion, differences of LDH in different tissues of the same individual organism, including man. Of potential import for the study of the evolution, classification, and differentiation of enzymes, such results suggest the possibility of defining more precisely the tissue of origin of the elevated serum levels. For example, by a comparison of reaction rates, using different analogues of DPN, liver LDH can be differentiated sharply from myocardial LDH as can also the enzyme derived from the lung. Studies are now under way to investigate the clinical application of these findings. Markert and Moller[18] have also reported differences in LDH of different tissues by electrophoretic technics as have Mansour et al., employing kinetic and immunologic data.[19] Vesell and Bearn,[20] employing starch gel electrophoresis for the fractionation of plasma, found three different bands with LDH activity (called "isozymes"). Increased activity levels in one of the three bands—the α-1 band—was found in a small number of patients with myocardial infarction, whereas the elevated LDH level in leukemia was associated with increased activity in a different band. The unsettled state of this methodologic approach is reflected in a recent report by Wroblewski et al.,[21] describing a characteristic plasma electrophoretic pattern of five "isozymes" of LDH (LD1 to LD5) in normal subjects. In 15 patients with acute myocardial infarction, an elevation of one component, LD5, was observed for 8 to 15 days after infarction and considered more specific for myocardial damage than total LDH activity. They reported further that an elevated LD5 was observed in certain cases with small or subendocardial infarctions at times when total plasma LDH was within the normal range. Although the preliminary reports are encouraging, the technic of starch block electrophoresis, in its present state of theoretical and practical development, does not appear sufficiently practicable or convenient for routine clinical use. Some modification of the currently employed, simpler photometric catalytic method—such as the substitution of different DPH analogues as suggested by Kaplan—would appear more promising. In any event, the concept of molecular heterogeneity, the demonstration of "different" LDH's contributing to the elevated serum levels, and the possibility of delineating the specific tissue source affords considerable promise of a major advance in the specificity and diagnostic accuracy of this (and possibly other) enzyme measurements in diseases of man.

Other Enzymes

In addition to studies of transaminase and lactic dehydrogenase, changes in other enzyme activities have been investigated in cases of myocardial infarction. To date none has proved as consistently accurate, sensitive, or helpful. Several may be considered briefly:

1. Malic dehydrogenase (MDH)—another widely occurring metallo-enzyme, catalyzing the important reaction of the citric acid cycle:

$$\text{Malate} + \text{DPN} \underset{}{\overset{\text{MDH}}{\rightleftharpoons}} \text{oxalacetate} + \text{DPNH}$$

Measurement of this enzyme activity is technically less ideal than that of LDH, requiring a 20-minute waiting period. Serum levels are comparably increased in both experimental and clinical myocardial infarction.[16, 22-25] In general the time course parallels that of transaminase, reaching a peak within 24 hours, dropping sharply thereafter. It is similarly nonspecific, being elevated in liver disease, muscular damage, hemolyzed serum samples, etc. There is no direct correlation with LDH levels in given cases and there appear to be no outstanding advantages of MDH measurement.

2. Aldolase. This enzyme catalyzes the reaction:

$$\text{Fructose 1-6 diphosphate} \rightleftharpoons \text{d-glyceraldehyde-3-phosphate} + \text{dihydroxyacetone-phosphate}$$

In one study, serum levels were increased in 11 of 17 patients with myocardial infarction. The level rose promptly, and returned to nor-

mal rapidly in a pattern similar to that for SGOT. In another study,[8] increased levels were found in 13 of 14 cases, with an unexplained secondary rise about 5 days after the first peak, unassociated with clinical evidence of extension of infarction or rise of SGOT.

3. Phosphohexose isomerase—a glycolytic enzyme, occurring in plants and tissues and serum of animals and man, it catalyzes the reaction:

Glucose-6-phosphate $\rightleftarrows$ fructose-6-phosphate

Again elevated values followed the pattern of transaminase values with a prompt rise, followed by a rapid return toward normal.[11, 23] Elevated values were found in liver disease, muscle damage, certain tumors, hemolyzed samples, etc.

4. Oxidase. Ceruloplasmin, the blue, copper-containing serum protein, exhibits oxidase activity with a number of substrates, most actively with p-phenylene-diamine. A high degree of correlation has been found among the total plasma copper level, the concentration of ceruloplasmin, and serum oxidase activity in normal subjects as well as in myocardial infarction, pregnancy, and chronic infections (increased levels) and in Wilson's disease and some nephrotic patients (decreased levels). Measurement of serum oxidase activity is by far the simplest test and is considered to reflect the others with sufficient accuracy for clinical purposes. Vallee[26] first demonstrated in 1952 a significant increase in serum copper levels in each of 12 cases of myocardial infarction, which rose in the first 5 days, reached a plateau in 5 to 11 days, and progressively returned to normal within 19 to 30 days. Rowell and Smith[8] found a similar pattern of increase in serum oxidase levels in 10 of 13 cases of myocardial infarction. Although the pattern of change permitted diagnosis at later time intervals, they noted that oxidase activity usually failed to show the secondary rise exhibited by the other enzymes in episodes of extension of the infarction.

Several recent studies have attempted to correlate multiple enzyme activities on the same samples. For example, in one series of 24 patients with recent myocardial infarction,[11] elevated values were found as follows: SGOT, 12 of 24; LDH, 23 of 23; aldolase, 11 of 17; hexose isomerase, 10 of 13.

SGOT, aldolase, and hexose isomerase increased rapidly to a peak within 24 hours, dropping rapidly toward normal; LDH elevations were the only persistent abnormalities up to 10 to 14 days. In another study,[25] comparing SGOT, LDH, and MDH in 30 cases, levels of all three enzymes increased to two to three times normal values; the SGOT returned to normal in 5 days, LDH and MDH persisted elevated for 10 to 14 days. Rowell and Smith[8] found SGOT increased in 28 of 28 cases, SGPT in 23 of 28, aldolase in 13 of 14, and serum oxidase in 10 of 13. Thus, it would appear at the present writing that the mainstays of laboratory diagnosis remain (1) SGOT with the advantage of very early confirmation and (2) LDH, technically easier and permitting evaluation over a longer time period.

Summary

The determination of the levels of activity of various enzymes in the blood or serum of man represents a major advance in the laboratory diagnosis of various disease states. The widespread body distribution of various enzymes at relatively large tissue activity levels in comparison to the small amounts normally in the circulation has, on the one hand, permitted the demonstration of diseased or damaged tissue by the resultant elevation of serum levels of activity. On the other hand, the generally large amounts of the clinically significant enzymes in heart, liver, skeletal muscle, kidney, brain, etc. has precluded the desired specificity of a laboratory test. At the present state of development, increases in circulating levels of various enzymes appear to be more sensitive indicators of tissue damage than previously available ones, such as the erythrocyte sedimentation rate and the C-reactive protein but it must be remembered that they are equally nonspecific. Any cause of tissue breakdown—trauma, infection, infarction, ischemia, neoplasia—may result in elevated serum levels, presumably by the release of enzyme from the damaged tissue. Thus, as with all laboratory tests, considered clinical judgment of the over-all picture re-

mains essential. Despite this limitation, demonstration of elevated serum levels of certain enzymes (the two most useful at this time being SGOT and LDH) serves, in the proper clinical setting, as a highly valuable indicator of myocardial necrosis; failure to observe this on serial testing is an important negative finding. The SGOT activity rises promptly after myocardial infarction, permitting early confirmation. LDH, simpler to measure, affords the advantage of a more persisting abnormality (up to 10 to 14 days after infarction). In most comparative studies, LDH measurements appear to afford a greater over-all positive correlation with the ultimate diagnosis. The rapid development of this area of knowledge has already increased the diagnostic armamentarium of the clinician. Recent promise of methods to increase the specificity of the results augurs well for the future.

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Surgical Treatment of Angina Pectoris

By MICHAEL E. DE BAKEY, M.D., AND WALTER S. HENLY, M.D.

SINCE Heberden's classic description[1] of the syndrome of angina pectoris in 1768, considerable effort by medical investigators has been directed toward this problem. Although these studies have enriched the literature and have added to greater knowledge and better understanding of the various aspects of coronary artery disease, the surgical approach to the condition has remained inconclusive and controversial. A number of factors probably account for this disputed and uncertain status of the surgical treatment of coronary artery disease. Among these, perhaps the most important is the fact that the natural course of the disease is often so highly variable, not only among different patients but even in the same patient at different periods, and may be greatly influenced by many factors, both intrinsic and extrinsic, as well as by medical therapy. It has long been recognized, for example, that significant coronary artery disease could be present at necropsy with little disturbance of cardiac activity during life. On the other hand, Sir William Osler[2] made the observation more than fifty years ago that in some fatal cases of angina pectoris there was little alteration in the heart or coronary arteries. Because of these and other variables and the consequent inability to provide a properly controlled study, precise and accurate evaluation of the clinical results of surgical therapy has been extremely difficult.

The basic pathologic lesion in coronary artery disease is atherosclerosis, which leads ultimately to narrowing or occlusion of the lumen by progressive intimal thickening, intimal ulceration, hemorrhage, or superimposed thrombosis. As a result of this occlusive process, the myocardial circulation is reduced to a variable degree, depending upon the nature and extent of the lesion and the degree to which intercoronary collateral vessel development takes place. Serious disturbances occur when the latter compensatory mechanism fails to meet the ischemic changes produced by the atherosclerotic process. One or more of the following effects may then take place: angina pectoris, myocardial infarction, or mechanism failure. Myocardial damage leads to fibrosis, congestive failure, aneurysm formation, ventricular septal defects, or external rupture.[3] These disturbances ultimately lead to variable degrees of disability, invalidism, and death.

Accordingly, surgical treatment of coronary artery disease has been directed toward relief of these adverse effects of coronary arterial insufficiency. A number of different methods and procedures have been proposed and applied for this purpose, but in general they may be classified as follows: (1) denervation of the heart for the relief of angina pectoris; (2) decreasing metabolic demands on coronary circulation by thyroidectomy; and (3) improvement of arterial circulation to the myocardium.

More than fifty years have elapsed since the first surgical attack was made on angina pectoris. This consisted in interruption of cardiosensory and motor pathways to the heart by sympathectomy, a procedure which was originally suggested by Francois-Frank[4] in 1899, and successfully performed by Jonnesco,[5] in 1916. While many experimental and clinical investigations have since provided a better understanding of the underlying anatomic and physiologic principles of this method of attack, its clinical value remains uncertain. Anatomic and physiologic studies have demonstrated that the sensory nerve

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Supported in part by grants from the American Heart Association, Texas Heart Association, and Houston Heart Association, and grants H-3137 and HTS-5387 from the National Institutes of Health, U. S. Public Health Service.

Dr. Henly is an Established Investigator of the American Heart Association.

endings of the heart and aorta are present in the myocardium, endocardium, and epicardium, and in the adventitia of the coronary arteries. The neurons to these sensory endings converge in the periarterial plexus of the coronary arteries, traverse the superficial and deep cardiac plexuses, and course in the middle and inferior cardiac nerves, which join the corresponding cervical ganglia of the sympathetic chain. Practically all of these outbound fibers then descend to the upper thoracic ganglia and finally reach their cells in the spinal ganglia by passing through the white rami communicantes into the central portions of the first thoracic and upper four or five intercostal nerves. The vasomotor efferent or accelerator impulses to the heart and coronary arteries differ from the sensory, and their actions and pathways are not so well understood. These pathways involve both vagal and sympathetic nerves, but the exact mechanism of their action in producing vasoconstriction and vasodilatation has been difficult to determine precisely.

Three general methods have been employed clinically to denervate the heart: (1) cervicothoracic ganglionectomy; (2) posterior rhizotomy; and (3) paravertebral chemical (alcohol) block of the upper four or five sympathetic ganglia. A more accurate and lasting effect is obtained by the first two procedures; they require a major operation, however, and are associated with an operative mortality of about 8 to 10 per cent.[6] Good results in terms of relief of pain, increase in work capacity, and improvement of general condition have been reported in 70 to 75 per cent of cases following all these methods, but there is no good evidence that survival expectancy is increased. It should be recalled that destruction of cardiosensory nerves and the protective alarm mechanism occurs concomitantly.

The procedure of total thyroidectomy to decrease the metabolic demands of the body for the treatment of coronary insufficiency is now only of historical interest.[7] It is of interest to observe that in 1937 Parsons and Purks,[8] following a collection of tabulated data from various sources, found that in a series of 133 cases in which thyroidectomy was performed for angina pectoris excellent results were obtained in 55 per cent and that 28 per cent were moderately improved. The operative mortality was almost 4 per cent. Hypothyroidism may be induced more easily and safely by the administration of radioactive iodine.[9] Good results in relief of severe angina pectoris have been reported in about 75 per cent of cases.[10, 11] Final evaluation of this therapeutic approach in terms of work capacity and longevity remains to be determined.

Direct and indirect surgical methods designed to improve the arterial circulation of the myocardium have been developed following a better understanding of the factors underlying myocardial ischemia. Certain physiologic principles and pathologic changes concerning coronary arteries are of considerable surgical importance. Functionally the coronary arteries are largely "end arteries." Although intercoronary communication may exist, collateral circulation from this source is usually not sufficient to maintain viability of the myocardium following sudden occlusion of a major branch of a coronary artery. In a slowly developing occlusive lesion, progressive increase in intercoronary collateral channels may take place and provide some protection to the ischemic segment of myocardium. Although arteriosclerotic change may be generalized, it commonly is segmental. Atheromata may occur anywhere in the coronary arterial tree, but points of vessel bifurcation are sites of predilection. Frequently the occluding lesion is segmental in nature, is less than 5 mm. in length, and often lies in the proximal larger arteries.[12, 13] Distally, a thrombus may or may not be present.

On the basis of these observations, investigators have been encouraged to develop surgical procedures designed to augment arterial bloodflow to the myocardium through increase in intercoronary collateral circulation or by restoring circulation in the involved coronary artery. These various surgical methods may thus be classified into two broad categories,

namely, indirect and direct approaches.

Among the former, a number of different procedures have been devised and employed both experimentally and clinically to increase coronary collateral circulation. These vary in complexity from the simple placement of an irritant such as talc or asbestos in the pericardium[14] or ligation of the internal mammary arteries[15-17] to the grafting of various vascular structures such as the pericardium,[18] omentum,[19] pectoral muscles,[20] lung,[5, 21, 22] and intestines[23] to the myocardium; the implantation of a systemic artery such as the internal mammary artery into a tunnel in the myocardium;[24] and arterialization of the coronary sinus.[25] Perhaps the most popular of these procedures is the Beck I operation, or some modification of it, consisting in abrasion of the epicardium by mechanical or chemical (phenol) means, partial ligation of the coronary sinus, the use of asbestos or talc poudrage, and mediastinopexy. In a series of 347 patients in which this type of procedure was employed during a period of approximately 4 years, Beck[26] reported an operative mortality of 6 per cent and a total mortality after discharge from the hospital of 9.2 per cent. Of the 295 patients who were still living at the end of this period, 32 per cent were classified as having an excellent result and 62 per cent a good result. Using a somewhat similar procedure on 57 patients, Thompson and Plachta[27] reported an operative mortality of 12 per cent with results classified as 90 per cent improved in 50 per cent of the cases and 75 per cent improved in 40 per cent of the cases. Advocates of this procedure have been able to demonstrate that it provides an increase in the survival rate of dogs following ligation of the anterior descending coronary artery and have contended that this is due to increase in intercoronary anastomoses. On the other hand Gage and his associates,[28] using an experimental procedure that produced gradual occlusion of the circumflex and anterior descending branches of the left coronary artery, were unable to demonstrate any beneficial effects of poudrage in terms of a decrease or delay in mortality or a reduction in incidence of gross infarction.

Particularly important in this connection and in the critical evaluation of these indirect revascularization procedures as emphasized by these authors as well as by Gregg and Sabiston[29] is the concept of whether or not they can produce an increase in collateral circulation above that produced by the disease itself.

Second to the Beck I operation in clinical popularity has been the bilateral ligation of the internal mammary arteries, frequently combined with poudrage or retrosternal neurolysis. This procedure was first suggested by Fieschi in Italy in 1939[15] and employed in a number of patients with coronary insufficiency by De Marchi, Battezzati, and Tagliaferro.[16] The pericardiophrenic arteries arising from the internal mammary arteries supply a significant quantity of blood to the pericardium and give origin to small vessels to the posterior wall of the left atrium. In necropsy preparations vascular communications are demonstrable between the internal mammary artery and the coronary circulation. In this country Glover and his associates[17, 30] employed this technic in the treatment of coronary arterial disease, reporting relief of angina in 68 per cent of patients with an operative mortality of 7 per cent. The simplicity of the procedure, the variable course of the disease, and the relatively low associated operative mortality undoubtedly account for the widespread acceptance of this procedure prior to adequate clinical or experimental evidence that this operation significantly altered myocardial blood flow. Sabiston and Blalock[31] and numerous other investigators in experimental studies have demonstrated no evidence of value in internal mammary ligation. Even under special laboratory conditions permitting an increase in flow in the ligated mammary arteries, no significant increase in retrograde coronary flow nor protection of the heart against coronary arterial occlusion could be demonstrated. The clinical results following sham operations, i.e., transection of the

sternum without mammary ligation, are as good as those receiving the ligation.[32]

In 1946 Vineberg[33] first proposed, and later he and other investigators demonstrated, that if a systemic artery such as the carotid, subclavian, or internal mammary artery were implanted in a myocardial tunnel, the artery would eventually form anastomoses with the terminal branches of the coronary arteries. These arteriolar communications tend to occlude by intimal and medial thickening in the normal heart; these obliterative changes, however, do not take place in an ischemic ventricle. Although these vascular channels remain patent and undoubtedly conduct some blood, flow studies have shown this magnitude of flow to be disappointingly small.[34, 35] Vineberg[36] in 1958 reported the results of this procedure in 59 patients. In 17 patients with angina pectoris at rest the operative mortality was 59 per cent. In 40 patients with less severe symptoms the operative mortality was 5 per cent, with 78 per cent markedly improved after surgery. The unpredictable augmentation of myocardial blood flow combined with the technical problems associated with a successful operation has prevented wide acceptance of this procedure for the present.

It should be noted that, experimentally, arterialization of the coronary sinus (the Beck II operation) affords the most effective protection against ventricular fibrillation following acute coronary occlusion.[26] The anastomosis of a systemic artery to the coronary sinus is, however, fraught with many technical difficulties, requires a second procedure to ligate the coronary sinus partially, and clinically has had an operative mortality of 15 to 20 per cent. The resulting beneficial hemodynamic changes are usually lost within 6 months after operation.

Numerous investigators have attempted to graft richly vascularized tissues upon the surface of the heart. At present it has been difficult to demonstrate conclusively a significant flow of blood from the graft to the heart wall. Each worker has stressed the importance of the epicardial barrier to these revascularization procedures. Removal of the epicardium by mechanical or chemical means allows for better surface revascularization.[37] There is no strong evidence that any of these vascular pedicles significantly improves the myocardial circulation. Attempts to revascularize the myocardium from within the ventricular chamber by means of small plastic T tubes implanted within the wall of the ventricle have not justified clinical application.[38, 39]

More recently, still another procedure has been introduced by Day and Lillehei,[40] consisting in the creation of a right-to-left shunt by anastomosis between the pulmonary artery and left atrium to lower arterial oxygen saturation and thus utilize the stimulation of hypoxia in the development of intercoronary anastomosis. Experimentally they were able to demonstrate a significant increase in intercoronary anastomosis within 1 month after operation and reported dramatic improvement in one patient in which this procedure was used.

The direct surgical approach is aimed at increasing arterial inflow through the coronary arteries by removal of the occlusive lesion or by anastomosis of a systemic artery to the coronary arteries distal to the occlusion. This approach is based upon the demonstration that patients with angina pectoris not infrequently have partial or complete occlusion of a major coronary artery in the proximal portions of the vessel, which is segmental in character with a relatively normal distal arterial bed.[12] In light of this evidence and the fact that effective methods have been developed for the treatment of similar segmental occlusive lesions in peripheral vascular disease, it was only natural to consider application of these procedures, such as resection and graft replacement, endarterectomy, the bypass graft, and the patch graft to segmental coronary occlusive disease. The feasibility of utilizing these procedures has been well demonstrated by an increasing number of investigators in clinical studies as well as in experimental animals.[41–53] In the clinical application of these procedures particular interest has been devoted to endarter-

Figure 1

Photograph showing bypass Dacron graft between aorta and left circumflex coronary artery in dog that maintained coronary flow satisfactorily following ligation of left main coronary artery.

ectomy following the original report of Bailey and associates[54] on its successful employment in 2 patients. More recently Kattus and his associates [55, 56] have reported their observations on a series of 11 patients suffering from incapacitating angina pectoris in which coronary endarterectomy was performed. Among the 5 patients surviving operation, results were considered excellent in 2, good in 1, and fair in 2.

Efforts to utilize the bypass graft principle by some form of systemic-to-coronary artery anastomosis have been predominantly, if not completely, experimental in nature. Some of the earliest attempts of this kind were reported by Murray and his associates,[50] who utilized the carotid artery as a free graft from the aorta to the left anterior descending coronary artery. Among 17 dogs in which this procedure was performed, 5 survived 2½ hours to 8 days without infarction. A higher rate of successful results was more recently reported by Thal and associates,[53] who anastomosed the left internal mammary artery to the left circumflex coronary artery over a glass cannula to permit blood flow during the anastomosis. Fifty per cent of the animals

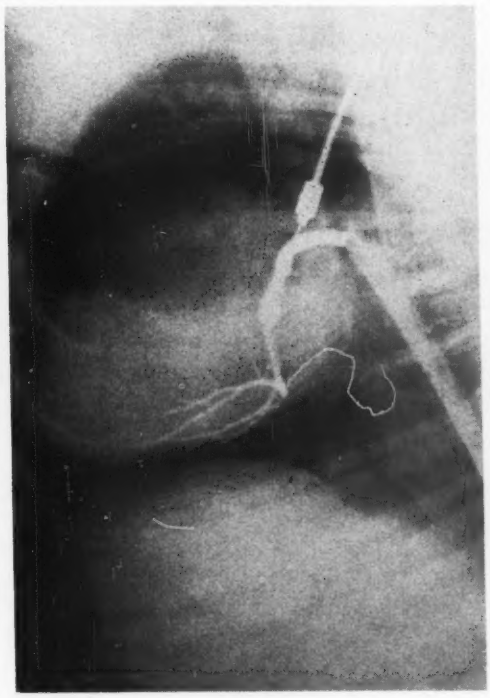

Figure 2

Coronary arteriogram made 24 hours after installation of bypass graft between aorta and left circumflex coronary artery demonstrating patency of anastomosis and filling of distal branches of circumflex artery.

survived the operation and the anastomoses were found to be patent 2 to 6 months later in 41 per cent. Somewhat similar results have been obtained in our laboratory with use of a knitted Dacron graft 3 to 5 mm. in diameter attached proximally by end-to-side anastomosis to the ascending aorta and distally by a similar anastomosis to the left circumflex coronary artery or the left anterior descending coronary artery with the use of a temporary internal shunt (figs. 1–3). Following completion of the anastomoses, the left main coronary artery is ligated, leaving the left ventriele dependent on the graft for its blood supply. These grafts have functioned in about 50 per cent of the cases.

Another procedure that has been studied experimentally in our laboratory is concerned

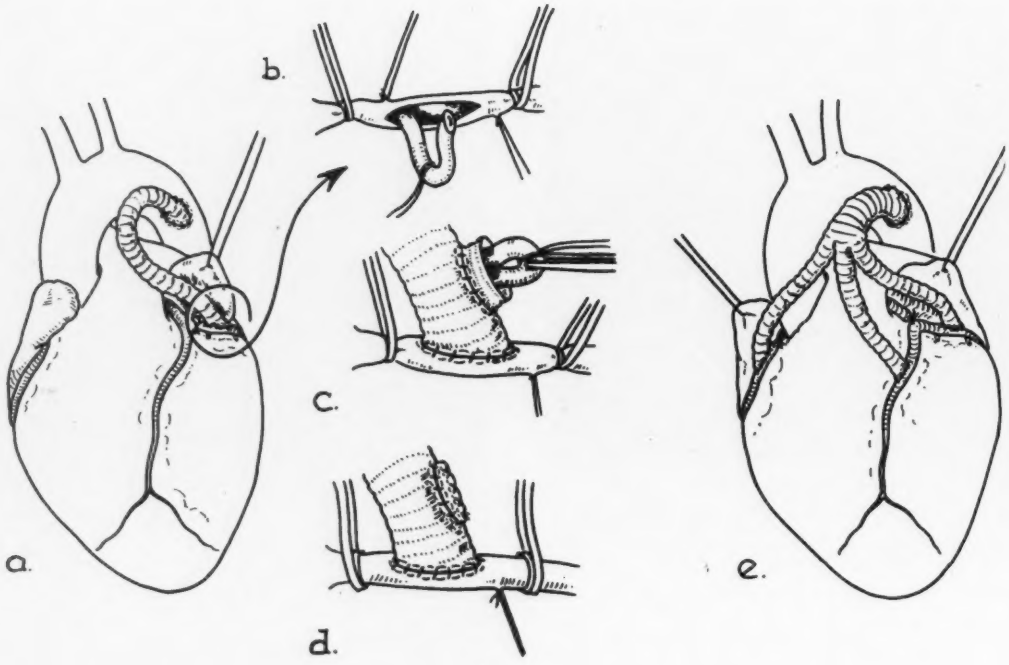

Figure 3

Diagrams depicting (a) *aorta-to-coronary artery bypass graft showing relationship to heart and aorta;* (b-d) *technic of insertion of internal polyethylene shunt and its withdrawal upon completion of anastomosis and* (e) *maintenance of entire coronary circulation by means of a trifurcated bypass graft.*

with the use of the patch graft.[57] We have used this procedure extensively in the surgical treatment of other forms of well-localized atherosclerotic occlusive disease with or without endarterectomy, and it has been found particularly valuable in lesions involving smaller arteries such as the internal carotid, vertebral, and popliteal arteries. These small patches of autogenous or synthetic graft material provide replacement of a sufficient part of the circumference of the artery to permit restoration of a normal lumen following arteriotomy. Successful application of this procedure to the coronary artery of dogs has been demonstrated in our laboratory (figs. 4–6). On this basis and from our clinical experience with its use in other small arteries, the patch graft would seem to have some advantages in the treatment of certain forms of well-localized coronary artery occlusive lesions.

It is thus apparent that a wide variety of surgical procedures has been devised and advocated for the purpose of improving myocardial circulation. Extensive investigations have also been done to evaluate the results of these procedures. In general the experimental design of most of these studies has employed one or more of the following criteria of benefit: (1) reduction in the amount of myocardial damage or in mortality rate in the group of animals having the experimental "protective" operation as compared with the controls following occlusion of a test artery, such as ligation of the left anterior descending coronary artery; (2) increase in retrograde coronary backflow in the experimentally treated animals as compared with the controls; and (3) morphologic evidence of new vessel formation following the experimental procedure. Evaluation of results of clinical application of these various proce-

Figure 4

Photographs illustrating (a) *arteriotomy of left circumflex coronary artery with internal polyethylene shunt in place.*

Figure 5

Appearance of vessel (fig. 4) after closure of artery with use of Dacron patch graft to avoid constriction of lumen.

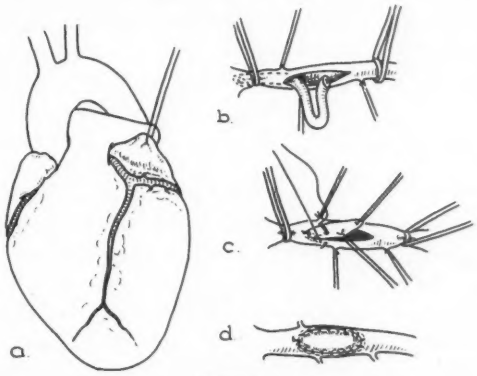

Figure 6

Diagrams (a-d) *depicting technical aspects of arterial repair of circumflex coronary artery with aid of internal shunt and small Dacron patch graft.*

dures has been based largely upon such criteria as survival rate, symptomatic improvement, and increased work or exercise capacity, with the patient serving as his own control. A wide range of operative mortality has been reported for these various surgical approaches from less than 5 per cent for the simpler procedures to over 50 per cent for the more extensive operations.

Efforts to assess the relative value of these various methods of surgical treatment of coronary insufficiency are fraught with many difficulties. As indicated previously, these are due in large measure to the highly variable course of the disease and to lack of precise and accurate criteria of benefit. Particularly striking is the remarkable similarity in the clinical results following these widely varying methods as reported by their respective advocates. This would suggest that they all possess some common factor or mechanism other than improvement in coronary circulation. This is well exemplified by the subsequent demonstration in well-controlled studies that certain procedures, such as ligation of the internal mammary artery, do not increase circulation.[58] Obviously the major difficulty in the critical evaluation of these methods of surgical treatment clinically lies in the lack of precise and accurate methods of demonstrating increased myocardial flow.[59, 60]

Despite these considerations there are reasons to believe that the surgical approach to this problem offers some promise.[61] Certainly for the relief of intractable pain uncontrolled by medical means, surgical methods by one of the simpler procedures, such as neurectomy

or chemical or mechanical de-epicardialization, may be employed with a low operative risk and high incidence of relief of pain. The most meaningful surgical approach to this problem, however, would seem to lie in those procedures designed to restore normal blood flow in the obstructed segment of the coronary arterial tree by methods, such as endarterectomy, bypass graft, or patch graft, that have proved so effective elsewhere. Better general acceptance and more widespread clinical application of these methods, however, await further developments along certain lines including particularly proper selection of patients for this purpose, diminution in the risk of operation, and good evidence of long-term maintenance of restored circulation. Precise and accurate localization of the lesion is probably the most important factor in proper selection of patients for operation. While certain tests may be of indicative value in this regard, in the final analysis angiography is absolutely essential for this purpose.[62-64] For this reason recent developments providing safer and improved methods of coronary arteriography are most encouraging.[65-71] Ready application of coronary arteriography will not only be of great value in the preoperative selection of patients for operation but will also provide more precise and accurate evaluation of the operative procedure by subsequent visualization of the coronary arterial tree. Progressive developments along these lines and increasing experience gained with application of these surgical procedures in segmental occlusive lesions in other small arteries should permit further refinements in technic and improvements in surgical management which would lower the operative risk to acceptable levels. There are sufficiently encouraging reasons to believe, therefore, that more intensive investigations of this approach toward relief of coronary occlusive disease are fully justified.

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CLINICAL PROGRESS

Management of the Cardiac Patient Requiring Major Surgery

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IT IS widely appreciated that the risk of death for cardiac patients undergoing major surgery is considerably less today than was the case 50 years ago. Greater surgical skill and improved cardiac management deserve much credit for this decrease in mortality. Of perhaps equal importance, however, have been the contributions from other areas. These include advances in anesthesia, the development of adequate blood bank facilities, improved understanding of fluid and electrolyte balance, and the effective use of chemotherapeutic agents. Finally, the fact that patients with clinical coronary artery disease can undergo major surgery with an additional mortality hazard of less than 4 per cent[1-3] reflects the value of attention to small details and of the institution of specific precautions to forestall catastrophe before, during, and following surgery.

The problem of cardiac risk during surgery has been a special pre-occupation of the medical service of the Beth Israel Hospital since the introduction of total thyroidectomy for the treatment of intractable forms of heart disease in 1930. This paper represents an attempt to develop from this accumulated experience of the past 30 years a working guide to the management of cardiac patients requiring major surgery.

The physician confronted with a cardiac patient needing surgical intervention must answer the following questions. Is organic heart disease actually present? What is the nature of the heart disease? What is the relation of the heart disease to the surgery? By what means before, during, and after surgery can the risk be reduced?

Problems in the Diagnosis of Organic Heart Disease

It is disconcerting to realize how many patients have been told they have heart disease that cannot be subsequently substantiated by complete cardiologic study. Among 631 patients referred to the Work Classification Unit at Bellevue Hospital in New York because of employment difficulties attributed to heart disease, 175 (28 per cent) were found on careful examination to have no recognizable cardiac pathology.[4] In most instances the erroneous diagnosis of heart disease had been based on a faulty interpretation of symptoms or signs that had been present for some time.

Fatigue and dyspnea should be carefully evaluated before being accepted as evidence of congestive failure. These symptoms may be found in patients with pulmonary disease, with malnutrition, or with anxiety. Precordial pain need not be cardiac in origin, but may be caused by neuritis, arthritis, or by the "effort" syndrome. Palpitation frequently is unrelated to heart disease. Essential

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Supported by research grant HTF-5235 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service, and by a grant-in-aid from the American Heart Association.

hypertension uncomplicated by demonstrable cardiac involvement, pulmonary embolism, and latent syphilis may each lead to an erroneous diagnosis of heart disease. Arrhythmias per se are not necessarily indicative of myocardial pathology: sinus arrhythmia, bradycardia, premature contractions, paroxysmal atrial tachycardia, fibrillation, or bundle-branch block may occur in the absence of demonstrable organic heart disease. Many systolic murmurs may be transient and innocent. Faint murmurs at the apex or base that do not radiate widely or louder murmurs that disappear on expiration are usually of no significance. In the presence of marked anemia or thyrotoxicosis, grade-III systolic murmurs and even diastolic murmurs may also be on a functional basis. Similarly, disturbances in heart sounds, such as accentuation of the first sound at the apex, a split in the second sound at the pulmonic area, or a third heart sound may be of no clinical significance. Many additional examples could be given of errors in the interpretation of other signs as well as of laboratory aids such as the electrocardiogram or the chest roentgenogram. It is perhaps sufficient to state that care and judgment are required to determine that heart disease is actually present before one can assess the added risk it may bring to a surgical procedure.

Nature, Extent, and Significance of Heart Disease

Once a diagnosis of heart disease has been established, its importance from the viewpoint of surgery can best be appraised by classifying the cardiac defect according to the nomenclature of the New York Heart Association.[5] Particularly in the older age groups the etiology frequently will be multiple. Perhaps the most significant aspect of the heart disease, insofar as it involves surgery, is the degree of incapacity suffered by the patient. This interpretation of incapacity involves not only an estimate of what the patient *can* do, but also what the patient *ought* to do.[5]

The relation of the heart disease itself to the contemplated surgery is too often overlooked. Occasionally the surgical problem concerns the cardiac pathology itself. Constrictive pericarditis, atrial septal defect, and mitral stenosis are common examples. In the presence of constrictive pericarditis, congestive heart failure becomes an indication rather than a contraindication for surgery. Not infrequently heart disease may masquerade as a "surgical" condition. Thus, acute myocardial infarction may simulate acute cholecystitis or peptic ulcer. Such possibilities must be seriously considered and excluded before undertaking any surgical procedure. The converse is also true, and many patients are denied necessary surgery for an acute abdominal catastrophe because of an erroneous diagnosis of acute myocardial infarction.

Relation of Congestive Heart Failure and Cardiac Pain to Cardiac Risk

After it has been determined that organic heart disease does exist, and after its nature, extent, functional significance, and relation to the surgical problem have been defined, it is possible to evaluate adequately the additional risk to the cardiac patient for whom surgery is contemplated. In 1928, Marvin stated, ". . . for purposes of anesthesia and operation, a heart that is damaged but that is carrying on an adequate circulation under normal conditions of life is the equivalent of a normal heart."[6] This statement, made over a quarter of a century ago, is still largely true today with the following notable exceptions: patients with angina pectoris or myocardial infarction, patients with aortic stenosis or regurgitation, and patients with atrioventricular block. These exceptions must be recognized because, while they may permit an adequate circulation under normal conditions, they may also lead to sudden death. The existence of a considerably increased risk must, therefore, be recognized in these patients even though none of the usual contraindications is present.

Other than these situations, the preoperative reduction of cardiac risk resolves itself,

from a practical viewpoint, into the appropriate treatment of congestive heart failure and the proper evaluation of cardiac pain.

Congestive Heart Failure

Preoperative treatment may be strikingly successful in converting even those patients presenting with gross congestive failure into less formidable risks. In addition to the underlying cardiac lesion, all factors that may have precipitated or aggravated the heart failure must be considered. These factors act by increasing the disparity between myocardial blood supply and demand. Some of these factors may be intracardiac, others extracardiac; several, moreover, may be functional in that they are not caused by organic disease (table 1). Recognition of these entities is particularly important, since several of them such as arrhythmias, anemia, and thyrotoxicosis are entirely reversible with appropriate therapy before surgery.

Table 1

Precipitating and Aggravating Factors in Congestive Heart Failure

Intracardiac	Extracardiac
Acute myocardial infarction	Pulmonary embolism
Acute rheumatic fever	Infection
Bacterial endocarditis	Asthma
Tachycardia*	Thyrotoxicosis
	Obesity
	Pregnancy
	Trauma
	Anemia
	Exertion*
	Emotion*
	Malnutrition
	Anoxia
	Cessation of cardiac therapy

*Functional

Angina Pectoris and Myocardial Infarction

In the evaluation of cardiac pain, the presence of stable angina pectoris per se is no deterrent to necessary surgery. The recent onset or recent aggravation of pre-existing angina pectoris, however, almost invariably indicates some change or imbalance in the coronary circulation.[7] Under such circumstances the stress of operation may precipitate myocardial infarction. The recent onset or increase in angina may itself be the prodrome of an episode of acute myocardial infarction. A recent myocardial infarction is a clear contraindication to surgery. As a general rule, elective procedures should not be undertaken until 3 to 6 months have elapsed after an infarction. Although the acute inflammation subsides by the third or fourth week, when the patient is usually ambulated, firm scar tissue is not present until the third or fourth month. Necrotic muscle and the outpouring of polymorphonuclear leukocytes are at their height during the first week (fig. 1). Although evidence of repair, manifested by the proliferation of pigment cells, plasma cells, lymphocytes, the removal of necrotic tissue, and the ingrowth of blood vessels and new connective tissue, occurs during the second, third, and fourth weeks after the onset of infarction, these processes are still going on for many weeks after the initial insult.[8] If necrotic material and active healing are still present, foci of irritability remain that may set off a fatal arrhythmia or precipitate fresh necrosis under the stress of a surgical procedure. These facts offer the best anatomic justification for prolonged bedrest during the first 3 to 4 weeks after an acute myocardial infarction and for delay in surgery until a firm scar has developed.

Other data, obtained from a study of cardiac rupture,[9] have shown that an acute myocardial infarction continues to change in extent for some time after its inception. Although the clinical picture indicates the onset of a myocardial infarction at a particular time, the entire infarct is not all of that same age. Rather, infarction is a continuous and progressive process with the simultaneous repair of old areas, the development of fresh necrosis, and the recovery of ischemic muscle.

Surgery and the Prognosis of Heart Disease

One of the problems that frequently arises in deciding on surgery in cardiac patients is the estimation of life expectancy with regard to the cardiac lesion itself. While it is reasonable to treat uterine prolapse or an abdominal

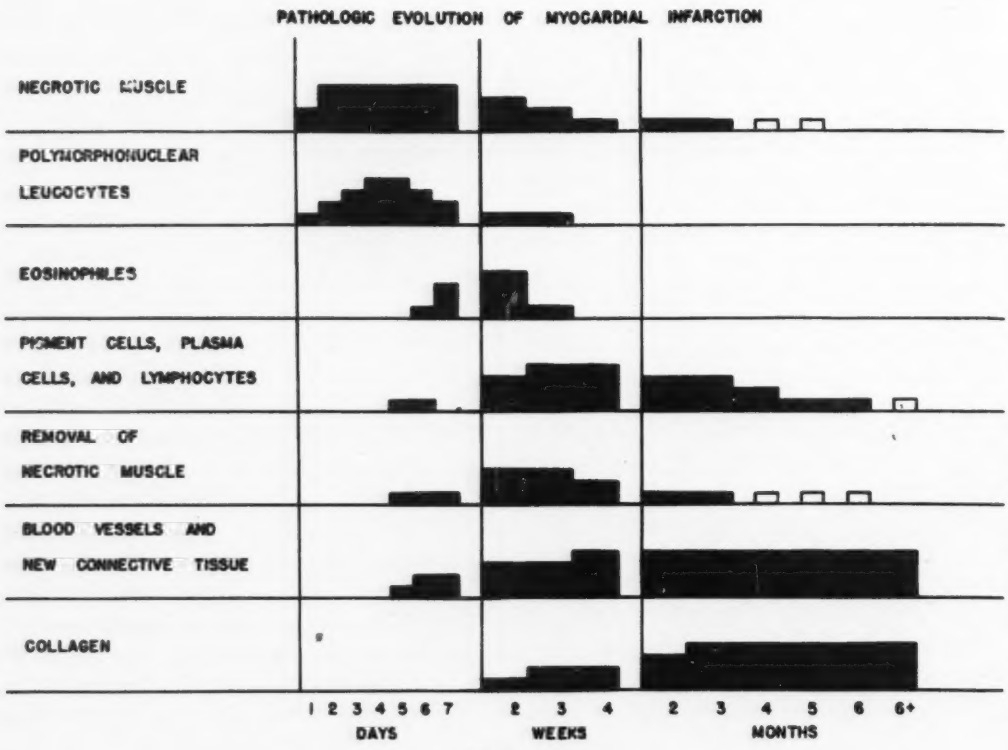

Figure 1

Schematic rearrangement by Dr. M. J. Schlesinger of pathologic data collected by Mallory, White, and Salcedo-Salgar[8] from a study of 72 hearts with myocardial infarction. The open boxes represent pathologic findings in small areas in individual specimens.

hernia by nonsurgical means in many cardiac patients, necessary surgery should never be denied because of a poor statistical prognosis of the heart disease itself. Although, in general, the average duration of life among patients with angina pectoris is from 2 to 8 years in different series, some individuals survive 15 or 20 years after the onset of cardiac pain.[10] Similarly, patients may live many years after the onset of congestive heart failure.[10]

The mortality curves of patients with angina pectoris and congestive heart failure admitted to the Beth Israel Hospital have demonstrated that the statistical prognosis is particularly somber in the early course, but less so in the later years of survival.[10] The difficulty that confronts the physician is that he cannot predict early in the course of angina pectoris or congestive heart failure which patient will survive for long periods of time. Consequently, angina pectoris and congestive heart failure are not adequate reasons, in themselves, for denying patients necessary surgery.

The Urgency of Surgery

The degree of cardiac risk accepted by a physician is often dependent on the urgency of the surgery under consideration. On the basis of our experience, elective surgery has been recommended for cardiac patients without angina pectoris, myocardial infarction, congestive heart failure, aortic regurgitation, aortic stenosis, atrioventricular block, or other serious arrhythmias (table 2). Cardiac enlargement, hypertension, or organic defor-

mities of the heart valves are not in themselves contraindications to elective surgery. For urgent surgery, such as carcinoma or repeated attacks of biliary colic, attempts should be made to control congestive failure, to stabilize angina pectoris, and, if possible, to delay surgery for weeks to months after acute myocardial infarction. In patients with aortic valve disease and arrhythmias, decisions concerning the time and extent of surgery must always be individualized. There are, of course, no absolute contraindications when lifesaving surgery is indicated such as in mesenteric thrombosis.

Table 2

Relative Contraindications to Surgery

Cardiac status	Type of surgery: Elective	Urgent	Life saving
Congestive failure	+*	Controlled	0†
Angina pectoris	+	Stable	0
Recent infarct	+	3-6 months	0
Aortic valve disease	+	±	0
Atrioventricular block	+	±	0
Arrhythmia	±‡	±	0

*Surgery contraindicated.

†No contraindication to surgery.

‡Recommendation for surgery based on specific findings in individual patient.

Cardiac Complications and Their Causes

The cardiac patient rarely, if ever, gets into difficulties from the surgery itself, but rather because of the complications attending the operative procedure. The four major cardiovascular catastrophes that may result from surgery are congestive failure, acute myocardial infarction, cardiac arrhythmias, and thromboembolism. In some instances latent rheumatic fever may become activated. The two commonest causes of these major cardiac disasters during or immediately following surgery are hypotension and anoxia. Usually they result from anesthetic difficulties or blood loss; each may aggravate the other, and either may produce myocardial ischemia. Hypotension can be prevented or promptly treated by adequate blood replacement at the time of blood loss, the avoidance of anoxia, the maintenance of an adequate blood volume by intravenous fluids, and the prompt use of appropriate sympathomimetic amines if the blood pressure begins to fall. Anoxia can be prevented by maintenance of a patent airway, adequate oxygenation, and an effective arterial pressure.

There are other less frequent complications that may also precipitate cardiac embarrassment. Fever and excitement increase cardiac work; dehydration may predispose to the development of thromboembolic phenomena; hypervolemia can cause pulmonary edema; hypoglycemia can precipitate myocardial infarction in patients with coronary artery obstruction; abdominal distention may interfere with venous return; and malnutrition may cause hypoproteinemia and vitamin B_1 deficiency, thereby precipitating or aggravating congestive failure.

Specific Measures That Reduce Cardiac Risk

Heart disease is usually a chronic affliction, and cardiac patients frequently have coexisting noncardiac pathology. Failure to recognize renal, hepatic, or pulmonary insufficiency, a bleeding diathesis, hypothyroidism, or latent diabetes may place additional burdens on the already compromised heart and thereby negate the efficacy of a surgical procedure. In addition to careful cardiovascular study, a comprehensive clinical evaluation is essential for the recognition of other diseases that may further embarrass the heart during surgery. There are, moreover, specific measures that may significantly reduce the hazards of surgery.

Drugs Prior to Surgery

In view of the increasingly wide variety of potent chemical agents now available for the treatment of disease, it is important that the administration of any such medications be known to the physician prior to surgery. Some patients may be using drugs regularly and not volunteer this information to the doctor. Many of these agents, such as rauwolfia and chlorpromazine, may potentiate the effect of preoperative medication.[11] Failure to appreciate the significance of anti-epileptic

medication, thyroid, pilocarpine, quinidine, digitalis, antihistamines, hypotensive or hypoglycemic agents, anticoagulants, or steroids may complicate or lead to the fatal outcome of an otherwise benign surgical procedure.

The problem of steroid therapy warrants special emphasis. Patients receiving corticosteroids must be given even greater amounts of these drugs during and following surgery than is generally recognized. Patients who have received steroids in the past may, after an interval of even 6 to 12 months, develop hypotension while undergoing surgery if corticosteroids are not administered during the operative procedure. If minimal amounts were given 4 to 6 months previously, little or no medication may be necessary. In contrast, patients who have received doses large enough to produce hypercorticism, may have continued suppression of the pituitary-adrenal axis for as long as a year following the cessation of therapy and may develop circulatory collapse on being subjected to the stress of surgery. Such patients, therefore, should receive intramuscular cortisone, 200 mg. daily beginning 48 hours before and on the morning of surgery and this drug should be continued postoperatively in decreasing amounts for 5 to 8 days. Hydrocortisone succinate should be available for intravenous use should hypotension occur during surgery. In the immediate postoperative period, hourly blood pressure measurements should be recorded to guard against cardiovascular collapse in these patients. It must also be recognized that patients receiving corticosteroids are very sensitive to morphine, so that it should be used cautiously, if at all.

Preoperative Medication

Every patient should be interrogated to determine whether or not he has ever had any idiosyncrasy to previous medication. Barbiturate excitement, for instance, may precipitate congestive failure in a susceptible individual. It is important to inquire carefully into any unusual reactions that the patient may have experienced in the past, especially from any of the medications contemplated before and after surgery. Moreover, noncardiac conditions such as emphysema, cirrhosis, or myxedema often require modifications in the preoperative use of barbiturates and opiates. Although this advice is more often honored in the breech, many untoward reactions would be avoided if all drugs that might be used while the patient was in the hospital were tested before operation, particularly if they had never been administered previously to the patient.

There may be unpredictable delays in the absorption of a preoperative sedative, and a large amount of such a drug given the evening prior to or even several hours before surgery may suddenly become effective during anesthesia, thereby producing undue depression. It is thus advisable to use light sedation and to administer immediately before surgery an adequate amount of morphine or meperidine to produce the desired degree of relaxation.

The digitalis glucosides are indicated preoperatively in the treatment of congestive heart failure, atrial fibrillation, and in some patients with a history of paroxysmal atrial tachycardia or atrial flutter. Somewhat more digitalis should be given to patients with atrial fibrillation or flutter than the minimal amount necessary to control their ventricular rates at rest. A given stress, such as exercise, causes a much greater rise in ventricular rate in patients with atrial fibrillation than in those with normal sinus rhythm.[12] This disproportionate rise can be greatly reduced by full digitalization leading to a slightly lower ventricular rate of approximately 70 at rest. The use of digitalis cannot be justified solely on the basis of the patient's age, blood pressure readings, or the mere presence of organic heart disease.

In patients with frequent angina pectoris, who are about to undergo surgery, the use of sublingual nitroglycerin prophylactically, 20 to 30 minutes before surgery, may be helpful.

Atropine is useful in lessening bronchial and upper respiratory secretions. It is not always appreciated, however, that, through its inhibitory effects on the vagus, an undue

increase in ventricular rate, especially in patients with atrial fibrillation, may result. It is desirable to anticipate this by the administration of test doses of atropine prior to surgery.

Reassurance

Anxiety may increase cardiac work. It is important to recognize that the majority of cardiac patients have a special apprehension toward impending surgical procedures. Such anxiety may frequently be reduced if the patient's own physician visits the patient in his room prior to the administration of the preoperative medication. Further reassurance can be provided if the physician can tell the patient that he will also be present at the operation.

Anesthesia

The choice of an anesthetic agent and of anesthetic technic for the cardiac patient should be considered carefully. "Ideal" anesthesia is an illusion, and attempts to establish fixed rules for the selection of anesthetic agents lead only to disaster. The selection of a program of anesthetic management should be based on the cardiac status as delineated by the cardiologist, the needs of the surgeon, the skill and experience of the anesthesiologist, and, wherein possible, the wishes of the patient. The following considerations are, however, helpful in reaching wise decisions in this area.

When feasible, local or regional field anesthesia should be considered because it causes the least increase in cardiac work. Aside from the possibility of vasomotor collapse or convulsions, particularly with cocaine and its derivatives, local anesthesia is associated with the least risk, if anxiety, discomfort, and pain can be avoided. The possibility of convulsions can be minimized by premedication with barbiturates. It is particularly important that no epinephrine be included in the local anesthetic mixture. Local anesthetic drugs are frequently packaged by pharmaceutical firms with epinephrine to provide a bloodless operative field through local vasoconstriction. It is the obligation of the physician to insist that, in cardiac patients, the local anesthetic be free of such sympathomimetic agents which, if absorbed systemically, can cause sudden death through cardiac arrhythmias in patients with pre-existing coronary disease.

Spinal anesthesia has certain advantages in patients with congestive failure from valvular disease.[13] Under such anesthesia orthopnea usually disappears. The attendant risk of hypotension in patients with diastolic hypertension and coronary artery disease, however, is significant though it can be prevented and treated by the intramuscular injection of vasopressor substances.

General anesthesia should not be undertaken without providing for an unobstructed airway. An endotracheal technic in certain types of surgery provides many safeguards for the cardiac patient.[14] Chloroform is a direct myocardial toxin, may produce fatal arrhythmias, and should no longer be used. Cyclopropane provides smooth, rapid induction, a pleasant recovery, and good relaxation, if it is supplemented, when necessary, by a muscle relaxant. Epinephrine is contraindicated at any time during the use of cyclopropane. The principal hazard of cyclopropane is the production of arrhythmias. These may possibly be diminished by the addition of a trace of ether to the cyclopropane anesthesia. Arrhythmias from cyclopropane are particularly prone to occur during induction. Cyclopropane anesthesia, therefore, may be initiated with thiopental sodium (Pentothal). In general, cyclopropane should be avoided in cardiac patients prone to arrhythmias and in patients with thyrotoxicosis.

Although Pentothal may depress the rate and depth of respiration and predispose to laryngospasm, it is an excellent drug for cardiac patients, if hypoxia is avoided and if relaxation is not required, as in the reduction of fractures or the incision and drainage of an abscess. Ethyl ether is an effective drug for patients with cardiovascular disease except when extreme relaxation is needed. Fluctuations in blood pressure are minimal at light and intermediate levels of anesthesia. To avoid hypotension from deep levels of

anesthesia, a light plane of ether anesthesia together with a muscle relaxant provides a good means of obtaining excellent relaxation.

Nitrous oxide alone cannot produce the desired amount of relaxation, particularly for abdominal surgery, without undue lowering of the oxygen content of the gas mixture. It is only safe and effective when combined with Pentothal and a relaxant such as succinylcholine. If muscle relaxants are used, adequate ventilation must be carefully maintained. This combination of anesthetic agents can be highly recommended for cardiac patients.

In practice, the experienced anesthesiologist by minute-to-minute observation and care can provide effective and safe anesthesia for the patient with heart disease. He can do this by inducing anesthesia quietly and without struggle, by maintaining anesthesia evenly and with adequate pulmonary ventilation, and by using anesthetic drugs in quantities that produce minimal changes in the patient and still provide adequate surgical exposure.

Cardiac Arrhythmias during Surgery

The physician should be prepared for the development of various arrhythmias during surgery. Some of these are of short duration and require no therapy. Many are directly related to hypotension or anoxia and, although responsive to pressor amines, are corrected only by eliminating the cause of the disturbance in pathologic physiology. If serious arrhythmias persist despite maintenance of arterial pressure and of oxygen saturation, drugs may be helpful in reestablishing a normal sinus rhythm. Supraventricular tachycardia and atrial flutter and fibrillation may be treated by carotid sinus pressure, intravenous lanatoside C (if the patient is not already receiving digitalis), or intravenous procaine amide (Pronestyl). Frequent ventricular beats or ventricular tachycardia may be eliminated by intravenous Pronestyl, beginning with a rate of 50 mg. per minute and gradually increasing the dose under direct electrocardiographic monitoring.

Cardiac arrest leading to death is one of the major accidents occurring particularly in patients with aortic stenosis, conduction defects, and coronary artery disease. Cardiac standstill is the usual mechanism of cardiac arrest during anesthesia. Ventricular fibrillation may occasionally be responsible. Preventive measures include the administration of atropine and the avoidance of overdigitalization, as well as the prevention of anoxia and hypotension. Constant observation of the heart by the anesthesiologist, using an oscilloscope or another monitoring device, is imperative in order to institute therapy immediately. Pounding the chest wall and needle puncture of the heart to stimulate cardiac action are indicated. The use of external stimulation of the heart through electrodes placed on the chest wall has been shown to be effective in the treatment of ventricular standstill. Impulses at 60 per minute and 3 milliseconds in duration are applied at 50 to 150 volts. All cardiac patients should have a cardiac monitor and an external electric pacemaker applied prior to the induction of anesthesia. Appropriate precautions must be taken to safeguard the patients from the hazards of electrical apparatus during anesthesia. If the patient has been monitored by oscillographic control and the mechanism is seen to be ventricular fibrillation, external countershock with an A.C. current at 250 volts or more for 0.15 second is effective. The heart either resumes normal beating or can be aroused from standstill by external electric stimulation. Most recently a simple method of applying pressure to the unopened chest for maintaining circulation until the cardiac beat is restored has been recommended.[15] If none of these measures is effective within 60 seconds of arrest, thoracotomy and manual massage of the heart are indicated. To salvage patients who develop cardiac arrest in the operating room, it is necessary that a prophylactic and therapeutic program be available *in advance* of the accident. Details of such a program have been published by Zoll and his associates.[16, 17]

Postoperative Drugs

Several drugs frequently used postoperatively may increase cardiac risk. Intestinal

distention occurs following numerous surgical procedures. In cardiac patients this complication may be treated by enemas or decompressing procedures but never by agents such as *pitressin*. This drug is one of the most potent coronary artery vasoconstricting agents and may cause severe cardiac pain, myocardial infarction, arrhythmias, and sudden death. In addition, oliguria may ensue. *Ergot* is frequently used to stimulate uterine contractions. It produces the same undesirable side effects as pitressin in patients with coronary artery disease and should certainly be avoided in all diabetic women. *Carbon dioxide* mixtures are still used empirically for the treatment of intractable hiccup. In concentrations above 5 per cent, cardiac output, rate, and blood pressure are increased and a cardiac catastrophe may be precipitated. It is desirable, therefore, to use carbon dioxide mixtures, if at all, only for short periods of time such as 2 to 3 minutes at 10-minute intervals. *Insulin,* if given in excess, may produce hypoglycemia: in patients with preexisting coronary disease, arrhythmias, congestive heart failure, or acute myocardial infarction may result. Therefore, in the treatment of the postoperative diabetic patient with insulin, it is usually desirable to permit a modest glycosuria. The goal of insulin therapy in the immediate postoperative period should be the prevention of acidosis rather than the elimination of hyperglycemia. *Epinephrine* is frequently used in the treatment of peripheral vascular collapse. This agent may produce severe cardiac pain, arrhythmias, and occasionally shock and death. There are other sympathomimetic amines such as phenylephrine (Neosynephrine), norepinephrine, and metaraminol (Aramine) that are better suited to the treatment of hypotension because they have less marked cerebral and less adverse cardiovascular effects.

Fluid and Electrolyte Balance

In cardiac patients excessive postoperative losses of fluid should be replaced to prevent electrolyte and acid-base imbalance which, if uncorrected, may lead to cardiac arrhythmias, digitalis toxicity, and impaired myocardial metabolism. If renal function is good, adequate postoperative hydration can be maintained by the administration of enough fluid to equal the volume of water lost plus the volume of urine required to prevent nitrogen retention. This goal can be accomplished by the administration of sufficient fluid to produce 1 liter of urine per 24 hours with the use of 5 per cent glucose in distilled water intravenously and by the resumption of oral intake as soon as possible. Large amounts of sodium-containing fluids may lead to congestive failure or pulmonary edema, even though these findings have been absent in the past. In patients with anemia, packed red cells may be preferable to whole blood. From studies of the influence of the rate of administration of intravenous fluids on cardiovascular dynamics in normal subjects,[18] it would appear that 15 ml. of fluids per minute represent a rate of fluid replacement in cardiac patients that should not produce pulmonary edema, unless salt is included.

Some cardiac patients, despite a normal blood urea nitrogen and an adequate preoperative urinary output, may have subclinical renal insufficiency. This state may be so aggravated by anesthesia, blood loss, dehydration, electrolyte imbalance, and congestive heart failure that a significant postoperative reduction in glomerular filtration rate may result. The possibility of such an alteration restricts the margin of safety ordinarily provided by the limited amounts of water recommended above.

Infection

Postoperative infections are particularly undesirable in cardiac patients because fever increases cardiac work and because bacterial foci may lead to the development of endocarditis, myocarditis, or pericarditis. Unfortunately, routine prophylactic chemotherapy is not effective in preventing infectious complications, and may, in itself, lead to superinfection with resistant organisms, disturbances in bowel function, and other evidences of drug intoxication. In patients with established valvular disease or other cardiovascular abnormalities predisposing to endocarditis, prophy-

Table 3

Cardiac Pathology in an Unselected Series of Injected Hearts (1936-1945)*

Age group	Normal M†	Normal F†	Myocardial hypertrophy 351-460 Gm. M	351-460 Gm. F	461+ Gm. M	461+ Gm. F	Valvular deformity M	Valvular deformity F	Coronary artery narrowing‡ 1+ M	1+ F	2+ M	2+ F	3+ M	3+ F	Coronary artery occlusion§ M	Coronary artery occlusion§ F	Total
1-10	11	6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	17 (11M, 6F)
11-20	9	8	1	1	—	—	3	4	—	—	—	—	—	—	—	—	26 (13M, 13F)
21-30	17	10	2	1	2	0	7	1	0	1	2	0	—	—	—	—	43 (30M, 13F)
31-40	12	26	3	2	6	1	6	2	3	2	5	0	1	0	1	1	71 (37M, 34F)
41-50	17	25	11	6	4	3	6	12	7	6	3	3	7	1	15	5	131 (70M, 61F)
51-60	28	25	15	11	9	3	5	3	27	12	12	10	10	5	47	11	233 (153M, 80F)
61-70	15	19	21	12	6	3	9	4	23	21	24	13	15	7	74	33	299 (187M, 112F)
71 +	7	5	8	2	1	2	3	4	15	14	21	15	12	10	48	24	191 (115M, 76F)

*Hearts reported as showing coronary obstruction may also have had valvular deformity or myocardial hypertrophy. The reverse was not true.
†M, male; F, female.
‡1+, 25 per cent reduction in the cross-sectional diameter; 2+, 50 per cent; 3+, 75 per cent.
§Refers to total occlusion of one or more coronary arteries.

lactic penicillin and streptomycin may be administered 24 hours before and for 3 days after operation. Such treatment may reduce the likelihood of bacteremia due to sensitive organisms, but the possibility of endocarditis due to resistant organisms must still be kept in mind in the postoperative period.

Bacterial prophylaxis, however, should not be limited to antimicrobial agents. Fever may be controlled by the use of aspirin and sponging with tepid water. Frequent turning of the patient may prevent bed sores. Pulmonary infection may be minimized by preventing the pooling of bronchial secretions through encouraging coughing, deep breathing, and, if necessary, the use of bronchodilators and sputum liquefiers. Prophylaxis against urinary tract infection should include the avoidance of the continued use of drugs that impair bladder function such as antihistamines and antispasmodics, the prevention of dehydration, and the aiding of the patient to void sitting on a commode, if unable to use a bedpan. Urethral catheterization should be resorted to only if simpler measures have failed to allow the patient to void. When indwelling catheters are required for prolonged periods of time, continuous irrigation of the bladder with ¼ per cent acetic acid may be of value in suppressing urinary tract infections.

If infectious complications occur postoperatively, appropriate cultures should be taken and specific antibiotic treatment begun promptly and in full dosage. The nature of the infection, the history of previous untoward reactions to chemotherapy, the results of cultures and sensitivity studies, and the clinical response to therapy should determine the choice of antibacterial agents.

Thromboembolism

The value of prophylactic measures in the prevention of thromboembolic postoperative complications is difficult to establish. Coumarin therapy has been safely administered during cardiac surgery,[19] and evidence of its effectiveness in the postoperative management of specific surgical problems has been indicated.[20] At the present time, however, the possibility of drug-induced hemorrhage in surgical pa-

tients is sufficiently great that it cannot be recommended as a *routine* operative or postoperative procedure even for cardiac patients in whom the likelihood of thrombosis is real. This is not to deny that in the future, anticoagulation may become the rule rather than the exception in the postoperative care of the patient with heart disease.

If anticoagulant therapy is indicated postoperatively, heparin is the drug of choice[21] and intravenous administration the preferred parenteral route.[22, 23] If anticoagulants are required within 72 hours of surgery, heparin may be given every 2 hours by intermittent intravenous injections in amounts that double the clotting time at 2 hours; after that time interval the drug may be given on a 4 hourly schedule.[23] Vein ligation should be limited to the treatment of septic phlebitis and to the management of nonseptic phlebitis when anticoagulants are contraindicated or have failed.

Frequent deep breathing, coughing, and turning in bed minimize the hazards of pulmonary atelectasis. Whether such activity as well as movements of the extremities and early postoperative ambulation prevent thromboembolism has not been established.[23] If such activity causes no harm to the patient, it is to be recommended because it diminishes vascular stasis—one of the factors known to predispose to thrombosis. Bandaging of the leg postoperatively with well-fitted elastic stockings, that do not act as tourniquets nor produce ulceration of the heel, can be recommended as a safe procedure in cardiac patients with an adequate peripheral arterial circulation. Such bandaging increases the rate of flow in the deep veins of the extremities. Whether it actually decreases the incidence of phlebitis has not been established conclusively.

The Distinction between the Cardiac and Noncardiac Patient

As the risk of surgery for the cardiac patient approaches that for the noncardiac, renewed interest will center about the causes of death attending surgery in individuals free of clinical heart disease, particularly over the age of 40. That deaths from heart disease play a significant role among such patients cannot be denied. Necropsy data have revealed a high incidence of coronary artery obstruction among patients without clinical heart disease.[10] In table 3, classified by age and sex, is the cardiac pathology observed among 1,011 unselected hearts examined by a special injection and dissection technic[24] at the Beth Israel Hospital from 1936 to 1945. In the fifth decade alone 60 per cent of male hearts exhibited coronary artery obstruction. Among all hearts from patients over the age of 40, less than one fifth were entirely normal. The majority of these patients died of noncardiac causes and many had no symptoms, signs, or laboratory evidence of heart disease.[25]

The implications of these data take on even broader significance with the realization that under the age of 40 and in patients with morphologically normal hearts, an occasional unexpected death may be cardiac in origin. Sudden cardiac arrest on induction of anesthesia for a diagnostic uterine curettage in an otherwise healthy 22-year-old woman may serve as an example. Since these cardiac difficulties cannot be predicted, the ultimate reduction of cardiovascular deaths in general surgery will be realized only when the precautions recommended for cardiac patients are applied to all individuals subjected to surgery.

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"We have good reason," he writes, "to be diligent in making farther and farther researches; for tho' we can never hope to come to the bottom and first principles of things, yet in so inexhaustible a subject, where every smallest part of this wonderful fabrick is wrought in the most curious and beautiful manner, we need not doubt of having our inquiries rewarded with some further pleasing discovery; but if this should not be the reward of our diligence, we are however sure of entertaining our minds after the most agreeable manner, by seeing in everything, with surprising delight, such plain signatures of the wonderful hand of the divine Architect, as must necessarily dispose and carry our thoughts to an act of adoration, the best and noblest employment and entertainment of the mind."—STEPHEN HALES, B.D., F.R.S. *Vegetable Statics*, 1727.

Dietary Fat and Its Relation to Heart Attacks and Strokes

Report by the Central Committee for Medical and Community Program of the American Heart Association*

CURRENT available knowledge is sufficient to warrant a general statement regarding the relation of diet to the possible prevention of atherosclerosis (Appendix I).

A heart attack, also called coronary thrombosis or myocardial infarction, or just plain "coronary," is almost always caused by atherosclerosis (arteriosclerosis or hardening of the arteries). Stroke, or apoplexy, is often caused by the same condition. The problem of preventing or retarding these diseases is, then, one of preventing or retarding atherosclerosis.

How Does Atherosclerosis Develop?

Atherosclerosis is a complex disease of the arteries. It is known that a number of factors influence or are related to its development. Among these factors are a high content in the blood of a type of fat called cholesterol, elevation of blood pressure above normal, presence of diabetes, obesity, and a habit of excessive cigarette smoking. Age, sex and heredity are also important.

What Types of Research Relate Diet to Atherosclerosis?

Many years ago a scientist fed cholesterol and other types of fat to rabbits. The blood cholesterol content increased and the rabbits developed atherosclerosis; that is, cholesterol and other fatty substances were deposited in the walls of the arteries. Many other animal species have been found to behave similarly. These animal experiments indicate that diet may be an important cause of atherosclerosis.

Global studies have shown that dietary habits of human populations differ. Evidence gathered from many countries suggests a relationship between the amount and type of fat consumed, the amount of cholesterol in the blood and the reported incidence of coronary artery disease.

Study of diets in the United States indicates that they usually contain large amounts of fat which account for approximately 40-45 per cent of the calories. In contrast, many populations in other parts of the world—for example, large groups in Asia, Africa and Latin America—eat food containing barely a third as much fat. The concentrations of cholesterol in the blood of such groups are much less than in those consuming the excess calorie and high-fat diets, and some reports indicate that heart attacks are correspondingly fewer. There are other differences in these diets that may also be of importance, such as the amount and type of protein and carbohydrate.

These and other research studies have given clues to the prevention of atherosclerosis by dietary means. A reduction in blood cholesterol by dietary means, which also emphasizes weight control, may lessen the development or extension of atherosclerosis and hence the risk of heart attacks or strokes. It must be emphasized that there is as yet no final proof that heart attacks or strokes will be prevented by such measures.

What Measures Reduce the Amount of Cholesterol in Blood?

Several ways of reducing blood cholesterol concentration are being studied at the present time. This discussion is limited to the modification of diet.

The amount of cholesterol in blood usually reflects the concentration of other fatty substances in the blood as well. If cholesterol is reduced, other fats in the blood usually decrease.

Several methods designed to reduce the amount of cholesterol in the blood have been suggested.

*The Central Committee for Medical and Community Program is the senior medical body of the American Heart Association and is chaired by A. Carlton Ernstene, M.D., of Cleveland, Ohio.

First, it would seem that the simplest way to reduce cholesterol in the blood is to eat less foods containing cholesterol. The problem is much more complex. If the amount of cholesterol in the diet is markedly decreased, but the caloric intake kept constant, the body may make more cholesterol from other substances, chiefly from other types of fat, sometimes nearly enough to make up for that which has been removed from the diet.

Second, reduction of the total caloric intake, by decreasing the amount of ordinary fat in the diet, usually causes reduction of the blood cholesterol concentration. Avoidance of excess fat in the diet also helps avoid obesity because one gram of fat provides 9 Calories, while one gram of protein or carbohydrate provides only 4 Calories. This does not mean that unlimited amounts of carbohydrate and protein should be eaten, for these, in excess, also lead to obesity and may also increase the level of cholesterol in the blood.

Third, the blood cholesterol concentration may also be reduced by controlling the amount and type of fat in the diet without altering caloric intake. Not all fats in the diet have the same effect on the amount of cholesterol in the blood. In the usual diet eaten in the United States, a large part of the fat is of the saturated type (Appendix II). Too much of this type of fat tends to increase the cholesterol in the blood. Considerable amounts of saturated fat are present in whole milk, cream, butter, cheese and meat. Coconut oil and the fat in chocolate also have a high content of fats of the saturated type. Most shortenings and margarines have less than half as much saturated fat, and the common vegetable oils have still less. When the intake of saturated fats is reduced, blood cholesterol levels usually decrease.

In contrast to the above food fats, many natural vegetable oils, such as corn, cotton and soya, as well as the fat of fish, are relatively low in saturated fats and high in fats of the poly-unsaturated type (Appendix II). When these fats are substituted for a substantial part of the saturated fats without increasing calories, blood cholesterol decreases. Finally, some food fats, such as olive oil, are more or less intermediate in saturation and have no strong effect one way or the other on the blood cholesterol.

These measures make it possible to attempt a considerable alteration in the cholesterol level in the blood with the use of acceptable diets.

Who in Particular Should Modify the Fat Content of His Diet?

A) Most persons in the United States who are overweight will find it profitable to reduce their total caloric intake. Reducing the amount of fat in the diet is one way to do this. In addition to the possibility that atherosclerosis will be prevented, obesity will certainly be controlled. Regular, moderate exercise, exemplified by walking, is also desirable.

B) Men with a strong family history of atherosclerotic heart or blood vessel disease, who have elevated blood cholesterol levels, an increase in blood pressure, are overweight and/or who lead sedentary lives of relentless frustration should consider modifying their diets. A diet moderate in calories and fat (about 25-35 per cent of total calories from fat) may be helpful for these coronary-prone persons. Substitution of poly-unsaturated for a substantial part of the saturated fat in the diet may also be a valuable addition to this program.

C) Those people who have had one or more atherosclerotic heart attacks or strokes may reduce the possibility of recurrences by such a change in diet.

> It should be borne in mind that moderate amounts of fat, particularly those containing an appreciable quantity of the poly-unsaturated type, are necessary for good health. Fat is an economical, and in limited amounts, a wholesome food. Food faddism of any sort should be avoided and significant changes in diet should not be undertaken without medical advice.

In Conclusion

The reduction or control of fat consumption under medical supervision, with reasonable substitution of poly-unsaturated for saturated

fats, is recommended as a possible means of preventing atherosclerosis and decreasing the risk of heart attacks and strokes. This recommendation is based on the best scientific information available at the present time.

More complete information must be obtained before final conclusions can be reached. Such information can be obtained only through intensified research into the causes and prevention of atherosclerosis—a program to which the American Heart Association is fully dedicated.

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*The Ad Hoc Committee on Dietary Fat and Atherosclerosis reported to the Central Committee for Medical and Community Program of the Association.

Appendix I

List of Recent Scientific References on Dietary Fat and Atherosclerosis

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Appendix II

Different Kinds of Fat in the Diet

Food fats and oils are made up of substances called fatty acids which are chemically combined with glycerol. In general, there are three different kinds of fats in our diet. These are called saturated, mono-unsaturated, and poly-unsaturated fats. All three types are usually present in any single food fat though in widely varying proportions. Thus, butter has about 55 per cent of saturated acids, 33 per cent mono-unsaturated acids, and 4 per cent poly-unsaturated acids. Corn, cottonseed, or soya oils contain in the range of 10-25 per cent saturated, about 25 per cent mono-unsaturated, and about 55 per cent poly-unsaturated fatty acids.

Not all fats in the diet have the same effect on the amount of cholesterol in the blood. Those high in saturated fat tend to increase the cholesterol in the blood, those high in mono-unsaturated acids have little effect, and those high in poly-unsaturated fats may cause a decrease. With vegetable oils this decrease is thought to be due largely to a poly-unsaturated fatty acid known as linoleic acid, and with certain fish oils to a variety of other poly-unsaturated fatty acids.

In the typical diet in the United States, a substantial part of the fat contains high levels of saturated fat—the fat in whole milk, cream, butter, cheese and meat. Coconut oil and the fat in chocolate are also high in saturated acids. Most of these fats are also low in poly-unsaturated fats. Most shortenings and margarines have less than half as much saturated fat and the common vegetable oils have still less saturated fat. Mono-unsaturated fat is present in appreciable amounts in most dietary fat. Poly-unsaturated fat is highest in the nonhydrogenated liquid vegetable oils; next in the lightly hydrogenated vegetable oils; then in margarines, shortenings, and lard; and is lowest in beef and dairy fat.

A considerable quantity of the fats and oils consumed in the United States are of the hydrogenated type. These fats and oils vary considerably in fatty acid composition depending on the extent of hydrogenation, a processing of the fat which retards the development of rancidity and can be used to convert liquid fats to a semi-solid or solid consistency. Hydrogenation also decreases the amount of poly-unsaturated fats depending on the extent of hydrogenation. Most of the solid margarines and shortenings made in this country by the process of hydrogenation are moderate in their saturated fat content and they are generally low in poly-unsaturated fats (10-15 per cent) though not as low as beef and dairy fat (2-4 per cent). It might be well for the manufacturers of fats and oils to indicate for the consumer by label declaration the approximate fatty acid composition of the final product in terms of the three main types of food fats—saturated, mono-unsaturated and poly-unsaturated.

BOOK REVIEWS

Cardiology: An Encyclopedia of the Cardiovascular System. Editor-in-Chief *Aldo A. Luisada.* New York, McGraw-Hill Book Co., Inc., 1959, 4 Vols., cloth, $100.00.

This imposing encyclopedia of almost 2,900 pages is the product of more than 250 contributors. Its purpose is to make available all current knowledge of the cardiovascular system. Recognizing the rapid advances in our knowledge, the editor-in-chief and publisher have issued the contents in a loose-leaf edition of four volumes in such a manner that new pages can be inserted readily.

As is inevitable with such an array of contributors, the quality of the various chapters varies considerably but is generally good to excellent. The editor-in-chief is to be congratulated on the degree to which he has been able to eliminate repetition and overlapping of information. In the first volume of over 500 pages, 45 authors describe the embryologic development and structure of the cardiovascular system. This is followed by discussions of cardiovascular function by more than 30 contributors. The subjects include the physiology of muscular contraction and metabolism of the heart, the cardiac output, heart sounds, blood pressure and its control, the abdominal, coronary, pulmonary, and cerebral circulations, cardiac reflexes, and the dietary requirements of the human body.

The second volume of more than 600 pages deals mainly with methodology, i.e., "Examination by means of the senses and related technical aids." The 60 authors include many outstanding international authorities. Some peripheral subjects are included such as "the psychological implications of the medical interview," "the clinical history," and "the general examination." Excellent discussions of radiology, electrocardiography, vectorcardiography, cardiac catheterization, and phonocardiography are presented.

The third volume of approximately 850 pages is a comprehensive treatise on clinical cardiology. The 80 authors discuss epidemiology, the manifestations of congenital and acquired heart disease, pericarditis, myocarditis, coronary heart disease, and the arrhythmias.

Volume IV of the series is a comprehensive description of therapy and of prevention and rehabilitation.

The primary function of this encyclopedia is for reference on specific subjects which any physician, whether he be cardiologist, internist, surgeon, may wish to study. The organization of the material has been ingeniously arranged to meet this need. In the future, a comprehensive index of all four volumes would obviate the necessity of looking up a given subject in each of the four indexes. The bibliographic references and index are excellent. With the rapid advances in our knowledge, the loose-leaf feature will be invaluable.

Ashton Graybiel in his foreword wisely comments, "In using this encyclopedia, the physician must let go of his inclination to be taught, and cultivate the art of selecting new items of information and fitting them into a frame of reference dictated by his needs. This method does require a capacity for mental independence and is effective only insofar as this is exhibited by those for whom the encyclopedia is intended. Admittedly a work of this sort represents a form of communication in which there is much redundancy. At what point will the evil of redundancy equal or exceed the good contained in the message? Herein lies a very real problem with which we should be concerned in the future." The editor-in-chief has controlled this factor admirably. Throughout are numerous cross references that attest to prior pruning of many of the articles. The prodigious effort in bringing these volumes to fruition attests his devotion to the task and his ability. The format and quality of text and illustrations are exceptional.

The American College of Cardiology and the five pharmaceutical firms whose generous grants made this publication possible are to be commended. This encyclopedia does not supplant the leading texts but is a valuable additional reference source that is recommended particularly for libraries.

HERRMAN L. BLUMGART, M.D.

Grundriss und Atlas der Elektrokardiographie. *Rudolf Zuckermann,* Leipzig, Georg Thieme, 1959, 660 pages, illustrated. D. M. 72, 15.

The third edition of this volume, as before, consists of three parts: (1) an outline of electrocardiographic principles illustrated with numerous diagrams; (2) an atlas of representative normal and abnormal tracings with an extensive discussion of their electrocardiographic and clinical features; and (3) an assembly of animal electrocardiograms, from arthropods to various mammalian species. The text has been enlarged and revised

with particular emphasis on vectorial interpretation, and new diagrams and case observations have been added. Compared with other monographs of similar size, this presentation is unique in its attempt to cover the teachings of the several German, Latin-American and North-American schools. Based on the extensive review and a good selection of old and recent literature—from quotations of original writings by Einthoven to a summary of recently gained knowledge concerning the source and distribution of electromotive forces of the heart—the different ways of interpreting normal variants and abnormalities of the electrocardiogram are presented. However, the author's views largely reflect his many years of affiliation with the Instituto de Cardiologia, in Mexico.

The unbiased reader will be impressed by the failure of the author to demonstrate convincingly the potentialities and pitfalls, as well as the proper place of electrocardiography in clinical cardiology. For example, much stress is placed on the possibility of recognizing specific cardiac lesions from deviations of the frontal and spatial axes of the different deflections. Yet diagrammatic simplifications of this approach in congenital anomalies, as e.g., on page 142, show so much overlap as to defeat the real diagnostic value of the electrocardiogram in these conditions. Precise infarct localizations read into some of the illustrated cases lack anatomic confirmation. In fact, even the diagnosis of an infarct remains highly questionable in some cases (page 344). Sometimes, it is difficult to follow the author's concepts, for example, when every T inversion is labeled "ischemic" or when terms are used such as "ventil plane without myocardium" (page 334). The space devoted to the picture of Siamese twins and their electrocardiograms perhaps could be more appropriately utilized for an illustration of simple hyperkalemia or hypokalemia in an adult. While several very complex arrhythmias of similar nature are presented without a clear interpretation, one misses mention or illustration of simple interpolated ventricular premature systoles. One instance (pages 514-515) of interpolated nodal extrasystoles is, in the opinion of the reviewer, erroneously labeled as parasystole.

The reproduction of diagrams and actual electrocardiograms is excellent. Unfortunately, however, many of the latter appear to be distorted by "overshoot" artifacts. As a whole, therefore, this volume may be a valuable addition to the library of an experienced cardiologist to serve as a source to round out his knowledge of international literature, as a collection of unusual human electrocardiograms, and as a basis for experimental work on various animal species. However, it cannot be recommended as an introduction for a beginner nor as a reference work for interpretation of the numerous problems encountered in day by day clinical electrocardiography.

ALFRED PICK

Electrocardiographic Technique: A Manual for Physicians, Nurses and Technicians. Ed. 2. *Kurt Schnitzer, M. D.,* New York and London, Grune & Stratton, Inc., 1960, 109 pages, 62 illustrations. $4.75.

This compact manual of instruction in the technic of obtaining an electrocardiogram is addressed mainly to technicians. As the author modestly states, he does not pretend to be the originator of any procedure described in this book, for similar accounts are available in the leading text books of electrocardiography and elsewhere.

Since the publication of the first edition, 10 years ago, the introduction of unipolar leads and other advances has necessitated thorough revision and expansion of the text. The main topics include a description of the electrocardiographic machine and its operation, the various artifacts that distort the electrocardiogram and their elimination, and mounting and filing of electrocardiograms. A brief chapter of six pages is devoted to the technics of phonocardiography, ballistocardiography, and the vectorcardiogram.

The recommendations of the Committee on Electrocardiography of the American Heart Association are presented in full. A few pages are devoted to a simple description of the heart and circulation. The format and illustrations are excellent. The book is warmly recommended as a manual for technicians and office assistants.

HERRMAN L. BLUMGART, M.D.

Pathology of the Heart. Ed. 2. Edited by *Sylvester E. Gould.* Springfield, Ill., Charles C Thomas, Publisher, 1959, 1138 pages, illustrated. $32.50.

The 20 contributors to this outstanding treatise have achieved a comprehensive delineation of the subject. The pathology of the heart is interpreted in its broader aspects and includes chapters on historical development, embryology, physiology, pathologic physiology, clinicopathologic correlations, cardiopulmonary disease, surgery of the heart, histochemical methods, and various technics used in the gross examination of the heart.

The appearance of this second edition after seven years, represents a complete revision of every chapter and the addition of five new ones. Each chapter is preceded by a detailed table of contents. Numerous excellent illustrations are used throughout the text, many of them in color.

Among the outstanding contributions are the deft delineation of the history of our knowledge

of the pathology of the heart, the lucid description of the physiology and pathologic physiology of the heart, the comprehensive portrayal in 237 pages of the various congenital malformations of the heart and great vessels, an unusually fine discussion of cardiopulmonary disease, and the chapters on the various lesions of the coronary arteries and myocardium.

The publishers are to be commended for the attractive format and superior reproduction of illustrations that enhance the usefulness of the text. The book is a superb reference source and is warmly recommended to all students of cardiovascular disease.

HERRMAN L. BLUMGART, M.D.

Acute Cardiac Pulmonary Edema. *Sigmund Wassermann.* Springfield, Ill., Charles C Thomas, Publisher, 1959, 123 pages. $4.25.

This monograph was published as a tribute to Dr. Sigmund Wassermann by a group of friends and admirers. The author was formerly with the First Medical Clinic of Vienna under Carl von Noorden and K. F. Wenckebach and later at the Vienna Heart Station under Hans Horst Meyer and Emil Zak. Since 1939 Dr. Wassermann has been a cardiologist in this country. His monograph reflects his extensive clinical experience. In his discussion of the pathogenesis of pulmonary edema he concludes, chiefly on the basis of personal clinical experience, that acute pulmonary edema is primarily due to reflex factors mediated through the autonomic nervous system. This concept, in his opinion, is supported by observations that in some instances pulmonary edema has responded promptly to carotid sinus stimulation. A good part of the monograph develops this thesis. Dr. Wassermann's therapeutic measures and medications for pulmonary edema are evaluated in terms of his neurogenic theory. There are many case reports that are also presented as supportive evidence.

The style and writing are rather difficult to follow particularly because of multiple medical references, chiefly from the older European literature. It should be noted that a number of important references are omitted, including reports by Weiss, Robb, White, and other more recent studies on the subject of pulmonary edema, paroxysmal dyspnea, and cardiac asthma. In summary, this monograph is of some interest to the clinician because of the background and experience of the author. It is not, in our opinion, otherwise noteworthy as a contribution to the subject of acute cardiac pulmonary edema.

O. ALAN ROSE, M.D.

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Atrial Septal Defect. An Investigation in the Natural History of a Congenital Heart Disease. *H. Gösta Davidsen.* Copenhagen, Munksgaard, Publisher, 1960, 225 pages, illustrated. D. Kroner 50.

Oxymetrie. Theorie und Klinische Anwendung. *Kurt Kramer.* Stuttgart, Georg Thieme Verlag, 1960, 206 pages, illustrated. DM. 39.60; $9.40.

Cardiac Emergencies and Related Disorders. Their Mechanism, Recognition and management. *Harold D. Levine.* New York, Landsberger Medical Books, Inc., 1960, 381 pages, 44 figures. $12.00.

Cellular Aspects of Immunity. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme* and *Maeve O'Connor.* Boston, Little, Brown and Company, 1960, 496 pages, illustrated. $10.50.

Proceedings of a Symposium on Central Nervous System Control of Circulation. Edited by *Ludwig W. Eichna, Donald G. McQuarrie.* Washington, The American Physiological Society, 1960, 311 pages, illustrated. $5.00.

Demonstrations of Physical Signs in Clinical Surgery. *Hamilton Bailey.* Baltimore, The Williams and Wilkins Company, 1960, 928 pages, 1142 illustrations. $14.50.

Visual Aids in Cardiologic Diagnosis and Treatment. Edited by *Arthur M. Master* and *Ephraim Donoso.* New York and London, Grune & Stratton, Inc., 1960, 216 pages, illustrated. $10.00

Treatment of Cardiovascular Emergencies. *Aldo A. Luisada* and *Leslie M. Rosa.* New York, McGraw-Hill Book Company, Inc., 1960, 122 pages, illustrated. $4.95.

Pathologie und Klinik in Einzeldarstellungen. *Frank Schaub.* Berlin, Springer-Verlag, 1960, 207 pages, illustrated. DM. 49.60.

Congenital Malformations. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme* and *Cecilia M. O'Connor.* Boston, Little, Brown and Company, 1960, 308 pages, illustrated. $9.00.

Human Pituitary Hormones. Ciba Foundation Colloquia on Endocrinology. Edited by *G. E. W. Wolstenholme* and *Cecelia M. O'Connor.* Boston, Little, Brown and Company, 1960, 336 pages, 86 illustrations. $9.50.

Embolic Dispersoids in Health and Disease. *Gus Schreiber.* Springfield, Ill., Charles C Thomas, Publisher, 1960, 85 pages, illustrated. $5.50.

ABSTRACTS

ATHEROSCLEROSIS

Berge, K. G., Achor, R. W. P., Barker, N. W., and Power, M. H.: Comparison of the Treatment of Hypercholesteremia with Nicotinic Acid, Sitosterol, and Safflower Oil. Am. Heart J. **58**: 849 (Dec.), 1959.

Among 10 patients with hypercholesteremia on an unrestricted diet, large doses of nicotinic acid were found to be more effective in lowering plasma cholesterol than either safflower oil or sitosterol. When nicotinic acid and sitosterol were combined in treatment, the observed effects were nearly additive. It is pointed out that from a practical point of view nicotinic acid is inexpensive, simple to administer, and does not require alterations in the patient's dietary habits. This drug may therefore prove to be of value in hypercholesteremia when the safety of its long-term use has been established.

SAGALL

Friedman, M., and Byers, S. O.: Deposition and Fate of Cholesterol in Ocular Aortic Implant and in the Aorta in Situ. Am. J. Physiol. **197**: 1019 (Nov.), 1959.

Aortic implants were placed in the anterior eye chamber of 30 rabbits subsequently fed excess cholesterol and cottonseed oil. After 3 months of such feeding, 7 of these animals were sacrificed, and their implants and also segments of their own aorta were analyzed for cholesterol. Two more groups of these rabbits were sacrificed 2 and 3 months, respectively, after their return to a cholesterol-free diet. It was observed that the aortic as the host's own aorta at the end of the cholesterol feeding period. This difference became even greater in animals that were sacrificed 2 months after cessation of excess cholesterol feeding, but were still hypercholesteremic. However, the ocular implants of rabbits examined 3 months after cessation of cholesterol feeding were observed to have lost almost all of their cholesterol, whereas the animal's own aorta continued to exhibit an unchanged excess of cholesterol. The findings suggest that the ocular aortic implant differs markedly from the aorta in situ in regard to its penetration and retention of cholesterol.

KAYDEN

Pilkington, T. R. E., Stafford, J. L., Hankin, V. S., Simmonds, F. M., and Koerselman, H. B.: Practical Diets for Lowering Serum Lipids. Brit. M. J. **2**: 23 (Jan. 2) 1960.

The serum level of Sf 0-12 lipoproteins (rich in cholesterol esters) is established by saturated fats, while that of Sf 12-400 lipoproteins (rich in neutral fat) is determined by the carbohydrate content of a diet. This implies that the serum cholesterol level can be reduced by restricting saturated fats from the diet. If the saturated fats are replaced by carbohydrate, the Sf 12-400 lipoprotein and neutral fats will rise. However if

unsaturated fats are used to replace the saturated fats this rise will not occur. By the use of an unsaturated fat diet, patients with ischemic heart implant gained almost twice as much cholesterol disease demonstrated lower levels of serum cholesterol, low-density lipoprotein, and Sf 0-12 and Sf 12-400 lipoproteins. This was accomplished more efficiently without loss of weight than when low-fat diets were used. Furthermore the unsaturated fat diet was less monotonous and was better accepted.

KRAUSE

BLOOD COAGULATION AND THROMBOEMBOLISM

Mersky, C., Gordon, H., Lackner, H., Schrire, V., Kaplan, B. J., Sougin-Misbashan, R., Nossel, H. L., and Moodie, A.: Blood Coagulation and Fibrinolysis in Relation to Coronary Heart Disease. Brit. M. J. 1: 219 (Jan. 23), 1960.

Healthy white men and white men with evidence of coronary artery disease were age-matched and studied relative to various coagulation factors. The patients with coronary disease differed from the control subjects only in having a higher plasma-fibrinogen level in the age group over 50. These same coagulation factors were studied in healthy rural Bantu men and in age-matched healthy urban white men. The Bantu had lower plasma-prothrombin and serum-factor-VII levels, better prothrombin consumption, and higher plasma levels of factor VIII. They also formed more plasma thromboplastin and their fibrinolytic activity was greater than in the control group. There was no difference found in thromboplastin generation when the Bantu was compared to the patients with coronary artery disease. Speculations are made on the significance of these observations in relation to atherogenesis.

KRAUSE

Preziosi, P., Bianchi, A., De Vleeschhouwer, G. R., and De Schaepdryver, A. F.: On the Pulmonary and Cardiovascular Effects of Warfarin Sodium. Arch. int. pharmacodyn. 123: 227 (Dec.), 1959.

In the isolated guinea pig lung, Warfarin was found to have no pneumodilator effect and did not antagonize the pneumoconstriction induced by various agents. These findings did not support the observations of Blumberg et al., who noted a bronchodilator action with the tracheal ring technic. The activity of the isolated guinea pig heart was not notably altered by Warfarin in doses of from 1 to 500 μg., whereas doses over 2,500 μg. produced a marked negative inotropic effect proportional to the dose. Intracoronary injection of 0.5 to 2 mg./Kg. of Warfarin produced an increase in coronary blood flow in dogs. Warfarin was found to be 10 to 20 times less potent than papaverine in this respect. Injection of 0.5 to 5 mg./Kg. of Warfarin into the peripheral end of the femoral artery of the dog produced an increase in femoral blood flow, which was also less pronounced than papaverine. These vasodilator effects were attributed to a direct myolytic action of Warfarin. Tone and motility of isolated rabbit duodenum and guinea pig colon were reduced by Warfarin in concentrations as low as 1.2×10^{-5} and 2.4×10^{-4}, respectively. Spastic contractions of the colon, produced by barium chloride or synthetic hypertensin were partly counteracted by Warfarin (4.4×10^{-4}).

BRACHFELD

CONGENITAL ANOMALIES

Dadswell, J. V.: Congenital Anomaly of the Left Circumflex Coronary Artery. J. Path. & Bact. 79: 204 (Jan.), 1960.

A case report is presented of a 72-year-old man who died of bronchopneumonia and at necropsy was found to have a congenital anomaly of the left circumflex coronary artery. The descending branch of the left coronary artery arose from the left posterior aortic sinus and pursued a normal course, descending in the anterior intraventricular groove to the cardiac apex. The circumflex branch arose from the anterior aortic sinus along with the right coronary artery by means of a common ostium and passed posteriorly to the left to reach the atrioventricular groove. The author reviewed the few reported instances of anomalies of this type and noted that since the greater portion of the posterior surface of the ventricle was supplied by the right coronary artery or the anomalous left circumflex artery, an occlusion of their common orifice would have been more severe than in a heart with a normal coronary distribution.

KARPMAN

Dammann, J. F., Jr., Thomson, W. M., Jr., Sosa, O., and Christlieb, I.: Anatomy, Physiology and Natural History of Simple Ventricular Septal Defects. Am. J. Cardiol. 5: 136 (Feb.), 1960.

Isolated ventricular septal defects were described in terms of their development, structure, and clinical features; and 9 illustrative case reports of young persons were presented. The defect is not detrimental to the fetus but commonly becomes symptomatic in infancy unless its diameter is small. Small defects are detectable principally by finding a long, loud, systolic murmur at the mid or low left sternal border with little or no other abnormality being observed. The manifestations of moderate or large (diameter over 1 cm.

per square meter of body surface) defects depend chiefly on the degree of right ventricular outflow obstruction and therefore the size and direction of the shunt. In infancy these defects usually produce a large arteriovenous shunt which leads to decided enlargement of the left side of the heart and commonly to heart failure. As the child grows the defect becomes relatively smaller and consequently the shunt and the danger of heart failure are likely to lessen. When the pulmonary blood flow is very high, the capacity of the arterioles to dilate is exceeded so that slight pulmonary hypertension often occurs. Later in childhood, even with less voluminous flow rates, the arterioles tend to narrow and their walls thicken resulting in pulmonary pressure rises that may reach systemic levels. In such situations, the arteriovenous shunt decreases and venoarterial shunting and cyanosis appear (Eisenmenger's syndrome). The electrocardiogram changes from that of left atrial and ventricular flow overloading to one showing predominantly right ventricular pressure overloading, and the roentgenogram discloses diminishing pulmonary vascularity and a smaller heart. Cardiac catheterization, previously important for diagnosis in general, is indicated at this time to distinguish this syndrome from the clinically similar one in which the right ventricular outflow obstruction is due only to muscle hypertrophy in this region. The need for surgical closure of the defect before the development of severe pulmonary hypertension was noted, and the value of thorough and frequent observation of the patient was stressed.

ROGERS

Grosse-Brockhoff, F., and Murtz, R.: Oxygen, Critical Pulmonary Flow and Critical Hemoglobin Concentration in Morbus Caeruleus. Ztschr. Kreislaufforsch. **49**: 33 (Jan.), 1960.

As a result of cardiac catheterization in 55 patients with cyanotic congenital heart disease, the following conclusions are made: The effective venous oxygen reserve (cc./min./sq.m.) was considerably reduced in spite of polyglobuly (20.3 Gm. average hemoglobin). The average effective pulmonary flow was 1.85 L./min./sq.m. while the critical flow was 0.95 L. The possible reduction of effective pulmonary flow to critical levels was 33-55 per cent. The hemoglobin concentration necessary to guarantee an oxygen concentration above critical values was on the average 11 Gm. per cent, while the concentration necessary to keep the oxygen concentration above reaction threshold was on the average 11 Gm. per cent. As most patients with cyanotic congenital heart disease have relative anemia, therapeutic blood-letting should be avoided as far as possible, and all diagnostic procedures causing physical strain, including angiocardiography and cardiac catheterization, should be carried out under careful circulatory control.

LEPESCHKIN

Imperial, E. S., Nogueira, C., Kay, E. B., and Zimmerman, H. A: Isolated Ventricular Septal Defects. An Anatomic-Hemodynamic Correlation. Am. J. Cardiol. **5**: 176 (Feb.), 1960.

The preoperative cardiac catheterization data in 26 patients with isolated ventricular septal defects were correlated with findings at open-heart surgery. The size of the defect was thought to be the major determinant of the hemodynamic changes, and analysis of these changes permitted an estimation of the defect's diameter. A higher right ventricular systolic pressure tended to accompany a larger defect, but the pressure correlated better with an index of defect diameter divided by maximum transverse heart diameter. The arteriovenous shunt size was related parabolically to the right ventricular systolic pressure. Defects of less than 1 cm. in size and those associated with right ventricular systolic pressures greater than 90 mm. Hg were considered to be unsuitable for surgery.

ROGERS

Liu, M. C., and Corlett, K.: A Study of Congenital Heart Defects in Monogolism. Arch. Dis. Child. **34**: 410 (Oct.), 1959.

Congenital heart disease was studied in 173 mongoloid children. Of the 51 patients who died, autopsies were completed on 44 and congenital heart disease was found in 36.4 per cent of the autopsied group. The mean age at death was 3.2 years, and the chief cause of death bronchopneumonia. Congenital cardiac defects were detected clinically in 11 of the 122 living mongols. A history of maternal illness was present in 11 out of 16 autopsy cases and 3 out of 11 clinical cases of congenital cardiac malformations. Higher birth weights and no premature births were found in the mongols with congenital heart disease, whereas no difference was found in birth rank or in parental age between the groups with and without cardiac defects. Among the various cardiac lesions, ventricular septal defects were the most common followed in frequency by atrial septal defects, patent ductus arteriosus, and then by a group of less common miscellaneous lesions.

KARPMAN

Luthy, E., Rutishauser, W., Hegglin, R., and Hegglin, M.: Arterial Oxygen Saturation and Dye Dilution Curves in Congenital Cardiac Malformations. Cardiologia **35**: 356, 1959.

Dye-dilution curves in right-to-left and left-to-right shunt, based on investigations in 20 cases of congenital malformation of the heart are reported.

In atrial septal defect a small right-to-left shunt was often found, which disappeared after inhalation of oxygen. In patients with a high ventricular septal defect a noteworthy finding was variations with respiration of arterial oxygen saturation; this was attributed to changes in position of the septum below the overriding aorta. The effect of the Valsalva maneuver on arterial oxygen saturation in the presence of intracardiac shunts is also described.

BRACHFELD

Morgan, B. C., Griffiths, S. P., and Blumenthal, S.: Ventricular Septal Defect. I. Congestive Heart Failure in Infancy. Pediatrics **25**: 54 (Jan.), 1960.

A history of congestive heart failure was obtained in 17 out of 125 pediatric patients with ventricular septal defects. In each case, the initial symptom of congestive heart failure occurred between 1 and 6 months of age; 10 of the patients had persistent heart failure and eventually died before the age of 1. Clinical and laboratory studies in these 17 patients provided evidence of large left-to-right shunts with an increase in pulmonary blood flow; there were no observations of prognostic significance which distinguished between those patients with ventricular septal defects who, after developing cardiac decompensation, adapted to their disease and survived, and those who progressed with a fulminating course to death. The authors state that the guarded prognosis of infants who develop congestive heart failure warrants consideration of surgical intervention. They concluded that exacerbations of decompensation after infancy were rare; patients who survived the first year of life did not succumb to complications of the defect in childhood.

KARPMAN

Pryor, R., Woodwark, G. M., and Blount, S. G., Jr.: Electrocardiographic Changes in Atrial Septal Defects: Ostium Secundum Defect Versus Ostium Primum (Endocardial Cushion) Defect. Am. Heart J. **58**: 689 (Nov.), 1959.

Electrocardiographic observations on 100 patients with surgically proved secundum type of atrial septal defect and on 33 with the ostium primum type of atrial septal defect are presented. An rsR′ configuration (with a QRS duration of less than 0.11 second) in lead V_1 was found to be the most reliable single electrocardiographic change in both varieties of atrial septal defects. This pattern is called "right ventricular outflow tract hypertrophy" and is thought to arise from actual hypertrophy or dilatation of this portion of the right ventricle rather than from an interruption of conduction in the right bundle branch. In a smaller number of patients, an Rs or qR pattern was found in lead V_1; in others, there was complete right bundle-branch block. These changes, however, did not help in diagnosing the type of atrial septal defect. In differentiating the secundum from the primum defect, the mean QRS axis and the rotation of the QRS vector loop were found to be of cardinal importance. True right axis deviation (mean QRS axis or vector more than + 100° rightward) was present in 81 per cent of the secundum defects and in none of the primum defects. In all 100 patients with secundum defect, the mean QRS axis fell between + 50° and 180° and the QRS vector loop was clockwise and below the isoelectric line (0-180°). Left axis deviation (mean QRS axis or vector more leftward than −30°) was present in 82 per cent of the ostium primum defects and in none of the secundum defects. The mean QRS axis fell between 0° and —100° in 90 per cent of the primum defects. In 27 patients with ostium primum defects and true left axis deviation, the QRS vector loop was rotated counterclockwise and was above the isoelectric line (0-180°). The terminal QRS vector fell between + 120° and 150° in 91 per cent of the secundum defects and between −60 and −140° in 91 per cent of the ostium primum cases. Following surgical closure of the secundum defect the R′ usually decreased significantly within 2 to 4 months. In the absence of such regression the possibility of incomplete closure of the defect or of the presence of irreversible pulmonary vascular changes should be considered.

SAGALL

Sterz, H., Schriener, B., Hubl, W., Hinrichs, R., and Rosanelli, K.: Diagnostic Difficulties in Ebstein's Disease. Ztschr. Kreislaufforsch. **49**: 67, (Jan.), 1960.

Three patients with Ebstein's anomaly of the tricuspid valve are described. One of these had typical findings of cyanosis, round right atrium, wide P waves, a wide late R′ in V_{1-3} designated as P′ and attributed to activation of the atrialized part of the right ventricle, and an early systolic extra sound attributed to contraction of this part. The second patient showed incomplete right bundle-branch block and the systolic extra sound with less characteristic other signs, but intracardiac electrocardiograms showed a zone with right atrial pressures and absence of an atrial intrinsicoid deflection; this is an important diagnostic sign. The third patient showed no characteristic radiologic findings and a QRS complex of normal duration with an R′ wave only in V_{4R}-V_{6R}, but an early systolic extra sound. The diagnosis in this patient was made when, during withdrawal of the intracardiac catheter, atrial pressure curves followed pulmonary artery curves directly, without ap-

pearance of right ventricular curves. This behavior is explained by displacement of the tricuspid valve opening toward the pulmonary artery.

LEPESCHKIN

CORONARY ARTERY DISEASE

Doyle, J. T., Heslin, A. S., Hilleboe, H. E., and Formel, P. F.: Early Diagnosis of Ischemic Heart Disease. New England J. Med. **261**: 1096 (Nov. 26), 1959.

Observations are reported concerning 1913 male employees of the State of New York, primarily white office workers, who were followed with periodic clinical examinations for 44 months with particular emphasis on their cardiovascular systems. Initially, it was found that 37 out of 1,000 suffered from ischemic heart disease. For the 44-month period of study the average annual incidence rate of ischemic heart disease was 8.5 per 1,000 per year with most of the new cases being manifested by myocardial infarction or angina pectoris and only about one sixth by an abnormal electrocardiographic response to exercise. Although extremes of diastolic blood pressure, of obesity, and of serum total cholesterol were found in individual cases, there was no correlation of these factors with an increased risk of developing ischemic heart disease. It is concluded that available clinical and laboratory technics do not permit accurate individual prognostication of the risk of ischemic heart disease.

SAGALL

Friat, J.: Difficulties in Coronary Flow in Myocardial Infarcts with Atrioventricular Block. Acta cardiol. **14**: 589. 1959.

Three hundred and twenty-six patients with myocardial infarction were divided into 2 groups: 220 patients with clinical and electrocardiographic data and 106 patients with anatomic information including coronary arteriography, dissection of the coronary arteries and spatial reconstitution of the infarcted area. Prolonged PQ conduction time was found in 18 per cent of the first group of patients and in 24 per cent of the second group. The frequency was almost identical in occlusion of the left anterior descending and right coronary artery. No particular pattern of arterial distribution was found. Septal and atrial arteries were generally visualized by coronary arteriography. Second- and third-degree block was found in 1.4 per cent of the first group of patients and in 5 per cent of the second group. Obstructing lesions of both right coronary and anterior descending arteries were always found, and they partially explained the gravity of the outlook in infarction associated with second- and third-degree block. The role of the anastomotic circulation is discussed.

BRACHFELD

Gorlin, R., Brachfeld, N., Messer, J. V., and Turner, J. D.: Physiologic and Biochemical Aspects of the Disordered Coronary Circulation. Ann. Int. Med. **51**:698 (Oct.), 1959.

Coronary circulation was studied in 50 patients by catheterization of the coronary sinus and measurement of coronary blood flow by the nitrous oxide technic. A second measurement was made following sublingual administration of nitroglycerin in 37 patients and duration exercise in 15. Of the group of 50 patients, 10 had normal hearts and 23 had the anginal syndrome. Coronary flow was shown to depend upon the need for oxygen by the heart, and this was related to the hemodynamic and metabolic factors at any moment. Flow was determined by aortic perfusion pressure, duration of diastole and vascular resistance. In the normal subject, coronary blood flow doubles following the administration of nitroglycerin, with a 50 per cent decrease in coronary vascular resistance. In the presence of coronary artery disease with angina pectoris, coronary blood flow shows little change with nitroglycerin; coronary vascular resistance is virtually fixed. It is suggested that the beneficial effects of nitroglycerin in patients with coronary artery disease is probably attributable to a diminution in the contractility of the myocardium and modification of cardiac venous return. The fall in cardiac output and fall in blood pressure represent a fall in cardiac work. In patients with angina and depressed S-T segments on exercise, myocardial ischemia was evidenced by a fall in coronary venous oxygen saturation and the appearance of both pyruvate and lactate in coronary venous blood.

KAYDEN

Mackinnon, J., Anderson, D. E., Howitt, G.: Preliminary Observations on Cavodil in Treatment of Angina Pectoris. Brit. M. J. **1**: 243 (Jan. 23), 1960.

Cavodil (beta-phenylisopropylhydrazine), a hydrazine analogue of amphetamine, is a potent inhibitor of monoamine oxidase. The action of cavodil is prolonged, and the effects of a single dose may last for 7 to 10 days. The use of this drug is reported in 28 patients with angina pectoris using the double-blind technic. Forty-one per cent of the group improved with cavodil alone and received no benefit from the placebo. In many instances improvement did not become apparent for 3 weeks. Only 1 patient improved with the use of the placebo alone. Side effects were mild and in no instance was it necessary to modify the regimen. The chief undesirable effects that did occur were 7 instances of mild transient dizziness and this was associated with postural hypotension in 4 instances. Five patients complained of a dry

mouth while on the medication. The results were encouraging and suggested that cavodil may become a useful drug in the management of angina pectoris.

KRAUSE

Snodgrass, P. J., Wacker, W. E. C., Eppinger, E. C., and Vallee, B. L.: Metalloenzymes and Myocardial Infarction. III. Lactic Dehydrogenase Activity of Serum—A Determinate Diagnostic Measure. New England J. Med. **261**: 1259 (Dec. 17), 1959.

Assays of the serum lactic dehydrogenase (LDH) were performed on 1,250 occasions on a total of 500 hospitalized patients. The results were studied in regard to the usefulness of this measurement in the diagnosis of acute myocardial infarction. The serum LDH activity was significantly elevated in the 28 patients in whom the diagnosis of acute myocardial infarction was confirmed by autopsy and in all of the 66 patients in whom the diagnosis was established by classic electrocardiographic criteria. In this series there were no false-negative results in every proved case of myocardial infarction. In most of these patients a significant increase of serum LDH activity was detected within 12 hours after the onset of acute infarction. Abnormal values persisted until the tenth day, with the maximum rise occurring from the second through the sixth day. Thus, an increased serum LDH activity was found to be strong confirmatory evidence of acute myocardial infarction when the disease was suspected. Normal LDH activities were found in those patients who clinically were thought to have acute myocardial infarction, but in whom the diagnosis was disproved by autopsy. Elevated serum LDH activity was not limited to acute myocardial infarction, but the presence of an abnormal LDH activity always denoted serious disease. It is of interest that in this series 7 of 11 patients with congestive heart failure, but without myocardial infarction, showed elevated serum LDH levels. The observations of this study warranted the conclusion that the serum LDH serves its most useful purposes when other diagnostic parameters of acute myocardial infarction are atypical and that the addition of this method to those currently employed should permit the accuracy for the diagnosis of acute myocardial infarction to approach 100 per cent.

SAGALL

Strandjord, P. E., Thomas, K. E., and White, L. P.: Studies on Isocitric and Lactic Dehydrogenases in Experimental Myocardial Infarction. J. Clin. Invest. **38**: 2111 (Dec.), 1959.

The pattern of serum enzyme activity after myocardial infarction reveals uniform elevations of the activity of lactic dehydrogenase (LDH), glutamic-oxaloacetic transaminase (GOT), and aldolase, but no elevation of isocitric dehydrogenase (ICD). The myocardium has been reported to be rich in ICD activity. Myocardial infarction was produced in dogs during open thoracotomy and in the closed chest after recovery from thoracotomy. Enzyme activity was determined in coronary sinus blood and in blood from the superior vena cava. The clearance from the serum of exogenously administered ICD and LDH in normal dogs and rabbits was measured and compared with the clearance from the serum in animals subjected to hepatectomy and nephrectomy. ICD is released from injured myocardium after myocardial infarction for a brief time; by contrast, LDH is released later than ICD and remains elevated longer. ICD is rapidly cleared from the circulation following injection, whereas the clearance of LDH is more protracted. The clearance of both these enzymes is not effected by any single organ. Injection of these enzymes into the vena cava and portal vein of dogs and into the vena cava of hepatectomized and nephrectomized dogs demonstrated similar clearance rates. ICD activity is transiently elevated during the first 24 hours following experimental myocardial infarction. The brief duration of this elevation is apparently due to the extremely rapid clearance of ICD and to the brief period of its liberation. If this brief period of elevation observed experimentally also occurs in patients with myocardial infarction, it presumably explains the clinical failure to demonstrate elevated levels of this enzyme after infarction.

KAYDEN

Walton, R. S.: Successful Cardiac Massage for Cardiac Arrest Following Coronary Thrombosis. Brit. M. J. **1**: 155 (Jan. 16), 1960.

A patient, who sustained an acute coronary thrombosis, collapsed and developed asystole. Simple measures of resuscitation were used unsuccessfully for 3 minutes. On the ward bed, after a proper intercostal incision was made and oxygenation provided, the asystolic heart responded following 10 minutes of cardiac massage. It began to fibrillate, and this mechanism was then converted to sinus rhythm by the use of intravenous 2 per cent procaine. The patient made an uneventful recovery without evidence of cerebral damage and was alive 9 months later. It was concluded that if cardiac arrest, as a complication of coronary occlusion, was due to disturbances of conductivity or "electrical instability" then all the heart needed was another opportunity to beat. This chance can possibly be provided by cardiac massage and a drug to reduce the irritability of the myocardium.

KRAUSE

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Bisteni, A., Sodi-Pallares, D., Medrano, G. A., and Pileggi, F.: A New Approach for the Recognition of Ventricular Premature Beats. Am. J. Cardiol. 5: 358 (Mar.), 1960.

Various types of premature beats seen clinically were reproduced experimentally in dogs. Distinction of supraventricular from ventricular beats depended on the location of the extrasystolic QRS in the cardiac cycle as well as on its morphology. Decreased QRS duration and aberrancy were observed in ventricular extrasystoles appearing later in the P-R interval, in contrast with those seen in the T-P interval, which nearly always had a QRS duration of greater than 0.12 second and a pattern of complete bundle-branch block. The summation of a supraventricular stimulus and a ventricular extrasystole was found capable of producing a morphologically normal QRS with duration under 0.10 second. Supraventricular premature beats arising late in the cardiac cycle produced QRS complexes morphologically the same as those of sinus origin. However, those developing early in diastole generated QRS complexes of first- or second-degree bundle-branch-block type (right or left). The authors believed that previously held diagnostic concepts of the site of origin of premature beats should be revised in view of these findings. ROGERS

De Balsac, R. H., Piot, C., and Bougaran, J.: Operative and Post Operative Electrocardiograms in Open Heart Surgery with Extracorporeal Circulation with and without Cardiac Arrest in Sixty Cases of Congenital Cardiopathy. Acta cardiol. 14: 561, 1959.

The operative electrocardiogram often was of little value in this study, since the surgeon could readily detect arrhythmias. In a few cases, however, the electrocardiogram was the only manifestation of the sudden appearance of a serious difficulty, such as atrioventricular dissociation or bundle-branch block caused by a suture. This was observed twice in the total series, but the catastrophe avoided justified the use of operative monitoring. These electrocardiographic signs are not necessarily specific for certain surgical maneuvers and may result from intracardiac excitation without any detectable anatomic lesion. Other findings, including a widening of the QRS complex, alterations in the S waves, lengthening of the P-Q or S-T intervals, and T-wave inversions could not be ascribed to a definite lesion. BRACHFELD

de Landero, C. A., Luzardo-Ramirez, G., Sanchez, J. M., and Sodi-Pallares, D.: The Mean Manifest Electrical Axes of Ventricular Activation and Repolarization Processes (AQRS and AT) in Congenital Heart Disease: Frontal and Horizontal Planes. Am. Heart J. 58: 889 (Dec.), 1959.

In a previous communication concerning the electrocardiogram in congenital heart disease a table of the distribution of ÂQRS in the frontal plane was presented as a valuable procedure for determining the main diagnostic possibilities. In this report further tables concerning the distribution of ÂQRS and ÂT in the frontal and horizontal planes individually and combined are given. Study of these 4 factors based on the spatial locations of ÂQRS and ÂT offers a simple method of diagnostic approach in congenital heart disease.

SAGALL

Féhér, J., Pileggi, F., Teixeira, V., Tranchesi, J., Lima, F. X. P., Spiritus, O., Chansky, M., and Décourt, L. V.: The Vectorcardiogram in Chronic Chagas Myocarditis. An Analysis of the Intraventricular Conduction Delays Associated with a Superiorly Oriented ÂQRS. Am. J. Cardiol. 5: 349 (Mar.), 1960.

Fourteen patients with Chagas myocarditis were selected for vectorcardiographic study because of electrocardiographic QRS complexes of 0.12 second or greater with a superiorly oriented ÂQRS. These patterns were commonly found with right bundle-branch block. Ten patients had vectorcardiograms showing complete right bundle-branch block; there was additional evidence of intraventricular conduction disturbance and loss of electrical forces (attributed to myocardial fibrosis) not revealed by electrocardiographic analysis. Vectorcardiograms of the remaining 4 patients presented signs of left ventricular hypertrophy but not of right bundle-branch block. In 2 of these patients the electrocardiographic diagnosis of left bundle-branch block was not confirmed, since the horizontal plane inscription of the QRS loop was counterclockwise and the delay was located predominantly in the terminal forces. ROGERS

Feruglio, G. A.: Intracardiac Phonocardiography: A Valuable Diagnostic Technique in Congenital and Acquired Heart Disease. Am. Heart J. 58: 827 (Dec.), 1959.

The clinical value of intracardiac phonocardiography was studied in 160 patients. The phonocardiograms were obtained from a barium titanate microphone incorporated into the tip of a specially designed catheter. The normal intracardiac phonocardiographic patterns as well as those obtained in a variety of congenital and acquired cardiac

disorders are described. The clinical value of this technic in diagnosis arose from the fact that by this method murmurs could be sharply located to that chamber or vessel that received the blood responsible for their production. The greatest practical help was found in the cases of congenital heart disease. Thus, with an uncomplicated ventricular septal defect a pansystolic murmur was recorded only within the right ventricle, and with patent ductus arteriosus a continuous murmur was recorded only within the pulmonary artery. These findings enabled a diagnosis of either of these conditions with certainty, even when oxygen studies and clinical signs were equivocal. The different patterns obtained on withdrawing the sound catheter from the pulmonary artery into the right ventricle enabled the differentiation of infundibular and valvular pulmonic stenosis. In atrial septal defect this technic confirmed the source of the murmurs and sounds as the increased flow across the tricuspid and pulmonary valves rather than in the flow-across the defect. With Lutembacher's syndrome a mid-diastolic or presystolic murmur in the inflow tract of the left ventricle was a diagnostic sign. This method also proved to be of some help in the cases of acquired heart disease so studied establishing the tricuspid origin of the apical systolic murmur in pure mitral stenosis, in differentiating between a mitral opening snap and a delayed pulmonary closure, and in defining right-sided gallop rhythm.

SAGALL

Hundt, H. J., and Schleimer, H. J.: The Incidence of Widening of the Atrial Wave in the Electrocardiogram and its Possible Relations to Coronary Sclerosis. Ztsch. Kreislaufforsch. **48:** 1120 (Dec.), 1959.

Of 3,078 routine electrocardiograms, 828 showed a duration of the P wave exceeding 0.12 second (0.11 second at heart rates over 100, 0.13 at those less than 60). The incidence of this widening increased continuously from the second to the fifth decade, in a curve which was parallel to that of the incidence of arteriosclerosis but showed a lag of about 1 decade. Both curves showed a decreased incidence in women. In the patients with widening of the P wave definite clinical signs of arteriosclerosis increased from 10 per cent in the fourth to 80 per cent in the seventh decade. In many patients widening of the P wave preceded the appearance of myocardial infarction or atrial fibrillation. In patients under 40 years of age widening of the P wave was seen in 93 of 1,112 cases. Of these, 17 had valvular disease; 10, hypertension; 11, infections; and 55, no apparent cause: of the latter, 22 had also an intraventricular conduction disturbance.

LEPESCHKIN

Lemmerz, A. H., Heigl, W., and Ferroni, E.: Highly Sensitive Phonocardiography with Amplitude Limitation. Ztschr. Kreislaufforsch. **49:** 19 (Jan.), 1960.

In patients with loud systolic murmurs, a sensitivity necessary for adequate amplification of other murmurs and sounds may result in overloading or in crossing over of adjacent channels. In order to prevent this, a limiting circuit is described that can be incorporated into the last amplification stage.

LEPESCHKIN

Littmann, D.: The Electrocardiographic Findings in Pulmonary Emphysema. Am. J. Cardiol. **5:** 339 (Mar.), 1960.

Electrocardiographic alterations were estimated to be present in up to 85 per cent of patients with pulmonary emphysema. Early in the course of the disease the electrocardiogram is within normal limits although the QRS and P axes tend to approach +90 degrees. As the emphysema progresses, the standard and precordial leads acquire S waves, and the P waves grow taller and more peaked. Right axis deviation of QRS proceeds to an indeterminate axis when the mean QRS vector appears to be directed backward and perpendicular to the frontal plane. The curious electrical axis alterations in advanced emphysema could not be explained on the basis of anatomic change in heart position and were attributed to altered extracardiac conduction caused by the insulating effect of emphysematous lung anterior to the heart. The clockwise axis rotation produced, in 2 to 3 per cent of patients, QS complexes in leads V_{2-3} that could be confused with those of myocardial infarction. The classical electrocardiographic pattern of right ventricular hypertrophy was found in 5 to 8 per cent of emphysematous individuals while right ventricular enlargement was present anatomically more commonly. Twelve illustrative case summaries with chest roentgenograms were presented.

ROGERS

Mazzoleni, A., Wolff, R., and Wolff, L.: The Vectorcardiogram in Left Ventricular Hypertrophy. Am. Heart J. **58:** 648 (Nov.), 1959.

Vectorcardiograms and electrocardiograms were obtained on 100 patients who had uncomplicated left ventricular hypertrophy and no clinical evidence of coronary artery heart disease. Qualitative and quantitative descriptions of the QRS and T loops and the RS-T junction are presented. Analysis of the results showed that a screening diagnosis of left ventricular hypertrophy could be made on the basis of QRS morphology, S-T segment displacement, T-wave configuration and orientation, QRS-T angle, and certain features of

the initial forces and terminal appendage. The data further showed that a definitive diagnosis of left ventricular hypertrophy could be made on the basis of 11 QRS measurements that proved to be frequently abnormal in left ventricular hypertrophy and only rarely abnormal in other conditions. In 91 per cent of the 100 cases, a diagnosis of left ventricular hypertrophy could be made employing only 3 of these 11 diagnostic measurements. It was concluded that in the diagnosis of left ventricular hypertrophy the vectorcardiogram is superior to the electrocardiogram.

SAGALL

Morse, R. L., Brownell, G. L., and Currens, J. H.: The Blood Pressure of Newborn Infants: Indirect Determination by an Automatic Blood Pressure Recorder in 20 Infants. Pediatrics **25:** 50 (Jan.), 1960.

The blood pressure of newborn infants was measured by means of an automatic recording device that utilized a crystal microphone in place of the stethoscope; the microphone was placed on the inner surface of a nondistensible blood pressure cuff. The mean systolic blood pressure was 71 mm. Hg (range 58 to 95) and the mean diastolic blood pressure was 52 mm. Hg (range 42 to 64).

KARPMAN

Raynaud, R., Brochier, M., and Morand, Ph.: Accidents during Left Cardiac Catheterization by Direct Puncture. Arch. mal. coeur **12:** 1374 (Dec.), 1959.

Of 275 punctures of the left heart, 121 showed no serious immediate incidents, but could not be followed; of the 154 patients followed in detail, 88 had no reactions, 3 developed shock necessitating interruption of the procedure, 5 had pneumothorax, of which 1 precipitated cardiac failure leading to death after 10 days. Hemoptysis appeared in 10 patients after left atrial puncture, especially after repeated attempts, fever of short duration occurred in 18, prolonged pain at the puncture site in 5, and subcutaneous emphysema in 1 patient. Multiple ventricular extrasystoles persisting up to 2 minutes appeared in 5, atrial fibrillation in 2, S-T depression in 2, and S-T elevation lasting 8 days after ventricular puncture in 1 patient. Hemopericardium appeared in 3 patients. In 1 of these, who was anticoagulated before the procedure, it led to death on the 5th day; this patient demonstrated that excessively low prothrombin concentrations should be avoided. In another patient the hemopericardium led to grave heart failure, which disappeared after paracentesis, and to subclavian venous phlebitis, after direct aortic puncture. It is concluded that puncture should be avoided in patients with grave cardiac failure, even if this has improved after treatment, and in those with thromboembolic disease. Mild anticoagulation makes puncture easier but marked hypoprothrombinemia should be avoided. The duration of catheterization plays no important role, but repeated attempts facilitate accidents. In general, transthoracic puncture of the left ventricle is better tolerated than posterior left atrial puncture or retrosternal aortic puncture.

LEPESCHKIN

Scarborough, W. R., Smith, E. W., and Baker, B. M., Jr.: Studies on Subjects with and without Coronary Heart Disease. Serum Lipid, Lipoprotein, and Protein Determinations and Their Relation to Ballistocardiographic Findings (A Preliminary Survey). Am. Heart J. **59:** 19 (Jan.), 1960.

Biochemical and ballistocardiographic data are reported on 165 normal subjects and 115 patients with coronary heart disease clinically evident by angina pectoris or remote myocardial infarction. The mean serum cholesterol value was significantly higher in patients with coronary heart disease but there was an age trend that resembled that in the normal subjects, namely, a progressive rise from age 20 to a maximum in the seventh decade. Protein and lipoprotein electrophoretic patterns revealed an increased beta lipoprotein and an increased or retarded alpha-2 protein as the most significant changes. In normal individuals lipid-protein abnormalities were more frequent as age increased, so that in the sixth to eighth decade they were present in about 50 per cent of the subjects. In patients with coronary disease lipid-protein abnormalities were detected considerably more frequently than in the normal subjects, especially in the age range from 30 to 59 years. In all clinically normal persons under 40 the ballistocardiogram was normal. As the age of the normal subjects increased abnormal ballistocardiograms were found more often, with a maximum of 100 per cent being abnormal in the eighth decade. In patients with coronary disease there was a similar trend, but abnormal ballistocardiograms appeared more frequently than in normal persons. Except for the mutual relationship to age there was no association between serum cholesterol levels and ballistocardiographic classification in normal individuals. In the coronay disease group it was only in the 30- to 49-year-old age range that an increased mean serum cholesterol could be correlated with an abnormal ballistocardiogram. In normal subjects and in young patients (30 to 49 years) with coronary disease, lipoprotein and protein electrophoretic abnormalities occurred more frequently in association with abnormal ballistocardiograms

than in those with normal records. It is concluded that the result of this study indicates that further study between changes in serum lipid proteins and circulatory function may be rewarding.

SAGALL

SURGERY AND CARDIOVASCULAR DISEASE

Thomas, G. I., Anderson, K. N., Hain, R. F., and Merendino, K. A.: The Significance of Anomalous Vertebral-Basilar Artery Communications in Operations of the Heart and Great Vessels. Surgery 46: 747 (Oct.), 1959.

A fatal case of brainstem ischemia is presented as a complication of cardiopulmonary bypass utilizing the left subclavian artery subsequent to ligation of the internal mammary and vertebral branches. Because of anomalous blood supply, the ligation of the left vertebral artery deprived the basilar artery of its major blood supply. A review of autopsy material in adults and children and a review of the literature indicated that the following anomalous communications exist. The right vertebral artery may have inadequate communication to the basilar artery in 3.1 per cent of specimens. Similarly, the left vertebral artery may have inadequate communication to the basilar artery in 1.8 per cent of specimens. In addition, there is a wide variation in the size of the 2 vertebral arteries. Therefore, the femoral route for arterial cannulation during bypass procedures is advocated to avoid the mortality associated with sacrifice of the vertebral artery. Appropriate precautions have to be taken in the Blalock-Taussig procedure, in tetralogy of Fallot, operations for coarctation, and resections of aneurysms of the thoracic portion of the aorta.

SHEPS

UNCOMMON FORMS OF HEART DISEASE

Broustet, P., Bricaud, H., Cabanier, G., Dallochio, M., and Cottin, D.: Concerning Two Cases of Chronic Cor Pulmonale as a Result of Obesity. Arch. mal. coeur, 10: 1140 (Oct.), 1959.

A very obese 47-year-old man without any other cardiac or pulmonary disease gradually developed somnolence, dyspnea, cyanosis, and signs of right ventricular failure. The vital capacity was reduced (65 per cent), the residual air increased (20 per cent), the arterial oxygen saturation reduced (87 per cent), and the carbon dioxide increased (66 mm.). Erythrocytes and the electrocardiogram showed marked tight axis deviation, tall R waves in V_1, deep S waves in V_6, and inverted T wave in leads II, III, and V_{1-4}. After dietary and diuretic treatment, as well as thyroxin, had led to a 20 Kg. loss of weight, all findings became more normal and the electrocardiogram showed only slight right axis deviation with normal T waves. Another patient, a 52-year-old man, showed similar findings. The right ventricular hypertrophy in these patients was attributed to pulmonary vascular constriction due to hypoxia as a result of inadequate ventilation combined with increased blood viscosity due to hyperglobulia.

LEPESCHKIN

Himbert, J.: Two New Anatomic, Clinical and Hemodynamic Observations of Primary Cardiac Amyloidosis. Arch. mal. coeur. 9: 1020 (Sept.), 1959.

Both patients (a 56-year-old woman and a 45-year-old man) showed large, immobile hearts, diastolic gallop, venous hypertension, hepatic enlargement, ascites, and leg edema. Cardiac catheterization disclosed reduced cardiac output, elevated pulmonary capillary, pulmonary arterial, right ventricular, atrial, and ventricular filling pressures with a "dip-plateau" configuration. The electrocardiogram showed progressive low voltage, QS complexes in the right precordial leads and inverted T waves in the limb and left precordial leads. All these signs are typical of constrictive pericarditis, which was the original diagnosis. The similarity is explained by the anatomic findings, which included destruction of myocardial fibers directly as a result of amyloid infiltration, indirectly as a result of stenosis or occlusion of peripheral arterioles by amyloid, and interference with normal contraction and distention of the remaining fibers, which were imbedded in the stiff amyloid tissue. The "angina of effort" shown by the patients could be due to coronary arteriolar stenosis; later it was accompanied by hepatalgia of effort. The amyloid nature of the cardiac involvement can be suspected in the presence of associated involvement of the tongue, skin or nodes, splenomegaly or hyperglobulinemia, but it can be proved only by means of biopsies of the muscles, liver, skin, or other organs. Treatment with anticoagulants or with cortisone or its derivatives seems to be contraindicated in amyloidosis.

LEPESCHKIN

MacGregor, G. A., and Cullen, R. A.: Syndrome of Fever, Anaemia, and High Sedimentation Rate with an Atrial Myxoma. Brit. M. J. 2: 991 (Nov. 14), 1959.

A case of right atrial myxoma, not diagnosed during life, is reported. Previously, various authors have published clues to aid in the diagnosis of intracardiac tumors. These include alteration

in signs and symptoms with changes in posture, recurrent episodes of syncope, systemic embolization without bacteremia, variability of heart murmurs, and progressive failure with rapid cardiac enlargement. The authors note the syndrome of fever, anemia, and rapid sedimentation rate in their case and in previously reported cases. The systemic reaction is possibly due to degenerative changes in the tumor, a common manifestation of myxoma.

KRAUSE

Rosen, S. M.: Puerperal Cardiomyopathy. Brit. M. J. 2: 5 (July 4), 1959.

The clinical syndrome of puerperal cardiomyopathy may consist of congestive heart failure, cyanosis, tachycardia, triple rhythm, emboli from both sides of the heart, and chest pain. Electrocardiographic abnormalities and roentgen evidence of cardiac enlargement are often found. Though the actual incidence of exacerbations is undetermined, there is a tendency toward recurrence with subsequent pregnancies. Pathologically, the hearts are soft and flabby and contain ventricular mural thrombi. Histologically, the lesions are degenerative rather than inflammatory, and the myocardium shows foci of disintegrating myocardial fibers. The disease is more common in twin pregnancies. The incidence of the disease is probably low and mortality may occur. No satisfactory cause for the degeneration has been discovered.

KRAUSE

Skanse, B., Berg, N. O., and Westfelt, L.: Atrial Myxoma with Raynaud's Phenomenon as the Initial Symptom. Acta med. scandinav. 164: 321 (1959).

The authors report the complete clinical history, physical examination, and laboratory and necropsy findings in a 15-year-old schoolgirl with a myxoma of the left atrium. Death was produced by a cerebral tumor embolus and was not antedated by any cardiac symptoms. The initial symptoms were those secondary to Raynaud's phenomena but a modified cold sensitivity test was negative. The authors hypothesize that the Raynaud's phenomena may have been secondary to the vasospastic effects of small peripheral tumor emboli.

KARPMAN

VALVULAR HEART DISEASE

Coelho, E.: Postoperative Physiopathologic Results in Mitral Stenosis. Am. J. Cardiol. 4: 163 (Aug.), 1959.

Two hundred patients subjected to mitral commissurotomy were examined clinically and by multiple laboratory technics for periods up to 3 years after surgery. Sixty-seven to 70 per cent improved sufficiently to return to normal life. Twenty-six patients developed mitral regurgitation; however, in 15 of these it was of slight degree and considerable subjective benefit followed surgery. Unsatisfactory results were due to inadequate commissurotomy in 3 patients, to restenosis due to rheumatic reactivation in 2 patients, and to arterial emboli in 3. Twenty-five had a postpericardiotomy (posteommissurotomy) syndrome, which was unrelated to the appearance of the left atrial biopsy or to recurrent rheumatism. Objective findings usually paralleled subjective betterment. This parallelism particularly applied to substantial reduction of the diastolic mitral gradient and the pulmonary wedge and arterial pressures, especially when these were very high preoperatively. Subjective improvement could not generally be correlated with roentgenographic changes, pulmonary function tests, or findings of lung biopsy. In some patients the clinical improvement was greater than that reflected by the objective tests, which included vectorcardiograms, ballistocardiograms, angiograms, phonocardiograms, and electrokymograms.

ROGERS

Eich, R. H., Staib, I., and Enerson, D.: An Experimental Evaluation of the Indicator Dilution Technique for the Measurement of Mitral Regurgitation. J. Clin. Invest. 38: 2035 (Nov.), 1959.

In an effort to evaluate the accuracy of the indicator dilution technic in measuring mitral regurgitation, an operative shunt was created in dogs between the left ventricle and left atrium, which could be controlled and used for many comparisons between open and closed shunts. Fifteen dogs were so prepared and the degree of mitral insufficiency was regulated to about 20 to 38 per cent of cardiac output. If control values were obtained first, the technic was satisfactory for detection of small amounts of regurgitation. In the absence of control curves, it was not possible to distinguish open from closed shunts. Furthermore, even with a control tracing it was not possible to quantitate the shunt. The authors state that the difficulties in the method are due to variations in volume, mixing, and washout.

KAYDEN

Ellis, F. H., Jr., Brandenburg, R. O., Callahan, J. A., and Marshall, H. W.: Open-Heart Surgery for Acquired Mitral Insufficiency. Arch. Surg. 79: 222 (Aug.), 1959.

Fifteen patients with relatively pure mitral insufficiency underwent open-heart surgery. In

2, there was some stenosis of the mitral valve, although insufficiency was the predominant lesion. Two patients were in class II, 9 in class III, and 4 in class IV of the New York Heart Association Classification of Cardiac Function. Hemodynamic data were obtained before and after surgery. Asystole was not induced as the beating heart was essential for the proper evaluation of the effectiveness of the operative procedure. At operation one third of the patients had ruptured chordae tendineae. The involved leaflet was markedly elongated and everted freely into the left atrium during systole. In the remaining patients, the posterior leaflet was usually retracted and deficient in tissue. A dilated mitral ring was found in 9 of the patients. The attack on the mitral valve was individualized. In the presence of a dilated ring, sutures were placed in the mitral annulus in the region of one or both commissures to narrow the mitral ring. Two methods were used in the correction of ruptured chordae tendineae. The flail leaflet was fixed to the left ventricular wall and mitral ring and thereby immobilized. It acted as a baffle against which the intact leaflet could close. Another method consisted of shortening the elongated portion of the leaflet and tightening its leading edge by insertion of plicating sutures. This increased the rigidity of the leaflet and prevented eversion during systole and contributed to valvular competence. In the absence of a dilated ring, when incompetence was caused by deficiency of tissue in the posterior leaflet, a roll of Ivalon was sutured under the leading edge of the posterior leaf. The anterior leaflet met the prosthesis during systole, and competence was achieved. Two patients failed to survive the operation, and a third died on the ninth postoperative day because of arrhythmia. Air embolism occurred early in the series in 2 patients. Two of the surviving patients did not have a murmur at the apex at the time of discharge, and the remainder had a soft apical murmur. Postoperatively there was a uniform decrease in pulmonary artery wedge and pulmonary artery pressures and in the pulmonary vascular resistance to normal or near normal values. The cardiac index increased from below normal to normal values. Indicator-dilution curves demonstrated improvement in the contour at the initial postoperative catheterization in all instances. Three patients have been operated on too recently for evaluation. One patient died suddenly in heart failure 2 months after operation. Another patient has had continuing severe congestive heart failure although considerably improved. The remaining 7 patients are clinically well 3 to 12 months postoperatively and have been classified functionally in class I. In 2 of 3 patients studied hemodynamically after several months there was evidence of some recurrence of mitral insufficiency. The long-term effectiveness of this operative procedure cannot yet be evaluated. At present the authors advise open-heart repair for patients with relatively pure mitral insufficiency when significant progressive functional disability is present.

SHEPS

Ellman, P., and Oliver, R. A. M.: Association of Cardiac Pulmonary Haemosiderosis and Fibrosis. Brit. M. J. **2**: 988 (Nov. 14), 1959.

It is commonly accepted that cardiac pulmonary hemosiderosis will result in fibrosis. Probably the deposition of hemosiderin results from pulmonary capillary hypertension, leading to repeated intra-alveolar hemorrhages or diapedesis of red cells, possibly from varicosities in the anastomoses between bronchial vessels and pulmonary arterioles. Two patients with mitral stenosis are presented in whom pulmonary hemosiderosis did not progress to fibrosis. In 1 patient the miliary chest pattern was present for 18 years but after successful mitral commissurotomy it disappeared. In the second patient with typical roentgen evidence of pulmonary hemosiderosis and a 30-year history of hemoptysis, a successful mitral valvotomy could not be performed because of a heavily calcified valve. The patient died from a cerebral embolus, and the lungs at autopsy showed heavy hemosiderosis but no evidence of fibrosis, macroscopically or microscopically. It is concluded the mitral-induced pulmonary hemosiderosis, seen by x-ray, is not a contraindication to mitral valvotomy. Indeed, successful valvotomy might result in gradual disappearance of the miliary infiltration in the lung.

KRAUSE

Korner, P. I., Thorburn, G. D., and Edwards, A. W. T.: Limiting Conditions in the Application of the Dye Dilution Method to the Quantitative Estimation of Valvular Incompetence. Clin. Sc. **18**: 321, 1959.

The dye-dilution method has been reassessed in relation to the quantitative estimation of valve incompetence. The paper shows that under clearly definable conditions in a circulation model, the dye-dilution method yields accurate quantitative estimates of the amount of regurgitant flow. When dye was injected close to the zone of incompetence in either aortic or mitral incompetence, good agreement beween estimated and actual backflows was obtained. With a rigid atrium, the effect of valve incompetence on the dye curve was to cause a difference between the estimated and the observed volume between the injection and sampling sites. Estimated backflow was consistently below actual backflow. Intraventricular

injection of dye in the presence of mitral incompetence also caused error in the estimation of volume and backflow. When dye was injected far from the site of incompetence, underestimations of considerable magnitude were observed with both aortic and mitral incompetence. When both valves of 1 ventricle were incompetent, the method did not give correct estimates of the total amount of valvular incompetence.

KURLAND

Merendino, K. A., Thomas, G. I., Jesseph, J. E., Herron, P. W., Winterscheid, L. C., and Vetto, R. R.: The Open Correction of Rheumatic Mitral Regurgitation and/or Stenosis. Ann. Surg. **150**: 5 (July), 1959.

The purpose of this paper was to describe certain relationships of the annulus-valve complex in the competent and incompetent valve and to describe posteromedial annuloplasty, an operative procedure found to be of value in the correction of mitral regurgitation. Physical signs of mitral regurgitation may be present long before serious disability appears. Once this occurs the course rapidly deteriorates. Superior dislocation of the mitral annulus and enlargement of the left ventricle increase the degree of mitral regurgitation. This results in increased length of distance between the attachment of the leaflets to the annulus and the attachment of the chordae tendineae to the ventricular wall. The operative procedure employed by the authors was to shorten this distance and thus decrease the degree of regurgitation. With the patient on a bypass and the left atrium emptied of blood, a decrease in regurgitation was effected by a posteromedial annuloplasty. Coronary arteries and veins were carefully avoided and the remaining mitral orifice was tested for 2-finger patency to avoid producing stenosis. In patients with pure mitral insufficiency the results were encouraging. When there was combined stenosis and insufficiency the results were less satisfactory because of calcification and marked deformity of the valves. The poorest results have been obtained in lesions associated with some degree of aortic insufficiency. However, it is felt that, when the latter is of minor degree, mitral annulus valvuloplasty should be attempted. Air embolism is always a problem and precautions to avoid this are mentioned. Clots have been encountered only in patients with stenosis. Thrombi have not been seen in patients with insufficiency. The chief indication for the operation is serious disability (class III or IV functional capacity) due to mitral regurgitation or combined stenosis and regurgitation of rheumatic etiology in an apparently inactive state. In the class III patient the risk of open mitral valve surgery, while high, is approaching the risk of blind commissurotomy. This procedure, however, is not indicated at this time in patients with pure mitral stenosis.

LEVINSON

Shenk, W. G., Jr., Portin, B. A., Leslie, M. B., and Andersen, M. N.: Hemodynamics of Experimental Acute Aortic Insufficiency. Ann. Surg. **150**: 104 (July), 1959.

It was possible to produce uniformly high degrees of aortic insufficiency in dogs by transventricular aortic valvulotomy with the Himmelstein valvulotome. Pressure and flow studies were carried out before and after aortic valvulotomy then repeated after placement of the Hufnagel prosthetic ball-valve in the descending aorta just distal to the left subclavian artery. Pulse pressures were increased from 35 mm. Hg before to 150 mm. Hg after aortic valvulotomy. The mean flow in peripheral arteries was reduced by more than 50 per cent. Cardiac output was also reduced. It might be anticipated that in a chronic state the ventricular ejection might be increased to maintain peripheral flow. Placement of the prosthetic valve resulted in decreased regurgitation from the descending aorta but increased reflux from the cerebral and brachial vessels. There was only slight decrease of reflux in 7 experiments. The mean flow in the descending aorta was increased but there was evidence of further diminution in flow to the cerebral vessels and probably to the coronary arteries. It would appear that successful surgical correction of aortic insufficiency awaits a suitable prosthetic valve.

LEVINSON

Soulie, P., Degeorges, M., Joly, F., Caramanian, M., and Carlotti, J.: A Source of Error in the Hemodynamic Diagnosis of Aortic Stenosis. Arch. mal. coeur. **9**: 1002 (Sept.), 1959.

A 27-year-old woman with increasing dyspnea of effort showed enlargement of the left ventricle, a diamond-shaped systolic murmur in the third and fourth left interspaces, a normal second sound, and a left ventricular hypertrophy and "strain" pattern with incomplete left bundle-branch block in the electrocardiogram. Catheterization of the right ventricle disclosed normal values, whereas that of the left ventricle showed a systolic pressure gradient of 80 mm. between left ventricle and aorta. During operation for aortic valvulotomy no stenosis could be found, and the patient died 5 hours after the operation. At autopsy marked hypertrophy and fibrosis of the left ventricle, with predominantly subendocardial and septal localization, were found; this caused diffuse stenosis of the entire outflow tract of the left ventricle. In contrast to typical valvular or subvalvular aortic stenosis, the ascent of

the aortic pressure curve was not delayed but synchronous with that of the left ventricular curve; however, it showed a secondary fall soon after its summit corresponding to creation of a stenosis by the contracting ventricular wall. Other points of differentiation were the absence of poststenotic aortic dilatation and the low localization of the murmur. A second patient, a 27-year-old woman, who showed almost exactly the same findings of functional or transient aortic stenosis, was not subjected to surgery.

LEPESCHKIN

Spitzbarth, H., and Dermentcoglu, A.: Hemodynamics in Systolic Aortic Valvular Murmurs of Sclerotic Origin. Ztschr. Kreislaufforsch. **48**: 906 (Oct.), 1959.

Of 92 out-patients 48 to 75 years of age, who showed physiologic arteriosclerosis, 34 had a systolic murmur in the aortic region, confined to the first half of systole, containing frequency components exceeding 70 c.p.s. and usually transmitted to the carotid region. Compared to the persons without murmurs, these persons had a higher incidence of aortic dilatation and elongation, higher systolic blood pressure and especially pulse pressure, and a much higher stroke volume and lower peripheral resistance, determined according to Broemser and Ranke. It is concluded that the murmurs are caused by an increased velocity of systolic ejection, combined with a sudden increase in cross-sectional diameter caused by dilatation of the aorta; both these factors facilitate eddy formation. Roughness of the aortic wall or valves secondary to atheromatosis is not a major factor, as murmurs may be absent when these changes are very pronounced. Increase of heart output by means of exercise or injection of Effortil and Suprarenine may cause systolic murmurs to appear in persons who ordinarily do not show them.

LEPESCHKIN

Uricchio, J. F., Sinha, K. P., Bentivoglio, L., and Goldberg, H.: A Study of Combined Mitral and Aortic Stenosis. Ann. Int. Med. **51**: 668 (Oct.), 1959.

The clinical and hemodynamic features of 141 surgically proved cases of combined mitral and aortic stenosis are reviewed. The group was composed of 52 men and 89 women and their ages ranged from 23 to 67 years. The findings in this group were compared to those in a series of 2,000 patients with pure mitral stenosis and to a series of 350 patients with pure aortic stenosis. Dyspnea and fatigue were present in 90 per cent of the patients with the combined lesions and two thirds of the group had edema. These observations were not different from those in patients with isolated aortic or mitral stenosis. The incidence of the anginal syndrome and of syncope in the group with combined lesions was one half the incidence in a group with isolated aortic stenosis. The rough murmur of aortic stenosis was present in all cases, and four fifths of the group had an abnormal aortic second sound. The murmur of mitral stenosis was also heard in almost every patient. Four fifths of the group had cardiomegaly by chest roentgenogram. The configuration resembled that seen in mitral stenosis rather than in isolated aortic stenosis. Electrocardiograms revealed a pattern of right, left, or combined hypertrophy in 40 per cent of the subjects. Cardiac catheterization was carried out in 31 patients. The calculation of valve areas showed no difference in the combined or isolated valve lesion. The cardiac output was less in the group with combined lesions compared with the group with an isolated lesion, but marked elevation of mean pulmonary artery pressure was not observed in the group with combined lesions.

KAYDEN

VASCULAR DISEASE

Bellman, S., Frank, H. A., Lambert, P. B., and Roy, A. J.: Studies of Collateral Vascular Responses. I. Effects of Selective Occlusions of Major Trunks within an Extensively Anastomosing Arterial System. Angiology **10**: 214 (Aug.), 1959.

Microangiographic studies of the rabbit ear were carried out before and as long as 7 months after ligature of the central artery and, in some instances, of 1 of its branches. Circulation was regularly maintained by means of enlargement of previously demonstrable collateral arteries. The enlargement was detectable 1 week after ligature and reached a maximum 2 to 3 weeks later when some of the collateral vessels also had become tortuous. The collateralization appeared to be due to hydrodynamic rather than ischemic forces, and mock ligations were followed by no change in the major arterial pattern. These findings contrast with those following occlusion of a porcine coronary "end" artery, where significant collateral vessels have been demonstrated 48 hours later, or following occlusion of an artery in a hamster cheek pouch in which collateral vessels may develop in sites where vessels have not previously been seen.

ROGERS

Carter, R., Vannix, R., Hinshaw, D. B., and Stafford, C. E.: Inferior Mesenteric Vascular Occlusion: Sigmoidoscopic Diagnosis. Surgery **46**: 845 (Nov.), 1959.

The clinical picture of left colon infarction consists of severe left lower abdominal pain and tenderness, usually accompanied by a bloody rectal discharge. In 3 patients in whom this picture was present, sigmoidoscopic examination revealed ischemic mucosal changes. These changes consisted of blue-black areas and represented early hemorrhagic infarction. These changes were seen in the rectosigmoid or higher, depending upon the condition of the blood supply.

SHEPS

Diaz, A. B., and Guzzy, P.: A Few Clinical and Hemodynamic Observations on Peripheral Arteriovenous Fistulas. J. Inst. cardiol. México **29**: 301 (May-June), 1959.

Eight patients with peripheral arteriovenous fistulas (5 traumatic and 3 congenital) are reviewed. The traumatic fistulas were seen in men whose ages ranged between 20 and 38, while the congenital fistulas occurred in women whose ages ranged between 16 and 23. The fistulas were located predominantly at the site of middle-sized vessels (subclavian, 2; femoral, 2; brachial, 1), and had been present an average of 4 years. At the precordial area the following features were present: accentuated sounds in 1 patient; a soft systolic apical murmur in 2 patients at the apex and a systolic and diastolic murmur, transmitted from the site of the fistula, in 3 patients. Electrocardiographically 3 patients showed "diastolic overloading" of the left ventricle, and 1 a suggestion of left ventricular hypertrophy. Radiologically 4 patients showed moderate cardiac enlargement. Clinically, 1 patient had left-sided heart failure; 1 complained of precordial chest oppression and palpitation with effort; 1 complained of short stabbing precordial pains, and 1 had vague complaints over the affected area. The diastolic pressure in the right ventricle was elevated but never above 10 mm. Hg. A slight gradient between the systolic pressure of the right ventricle and the pulmonary artery was noted. The cardiac index was elevated. The pulmonary pressure was decreased in 2 patients when the fistula was compressed. There was an evident decrease in flow through the fistula when the area was compressed, as proved by the fact that the venous blood distal to the fistula became less saturated following this compression.

BRACHFELD

Elliot, J. A., McKenzie, A. D., and Chung, W. B.: Ruptured Abdominal Aortic Aneurysm. Surgery **46**: 605 (Sept.), 1959.

Experience with 28 patients with ruptured abdominal aortic aneurysms is reviewed. Four patients were considered inoperable. Three patients died during the course of operation. Twenty-one had aneurysms resected and replaced by a graft. There were 9 survivors beyond the 1 month postoperative period. When the diagnosis was difficult as in some obese patients, roentgenograms of the abdomen, and in particular a lateral view, often outlined the aneurysm. Operative technic and management is described in detail. The early complications included impaired circulation to the legs, renal shut-down, and other vascular complications. Wound infections were frequent. Two patients died of ulceration of the proximal anastomosis into the duodenum, with fatal hemorrhage, 6 months and 33 months postoperatively. The cases are reviewed in detail.

SHEPS

Feruglio, G. A., Bellet, S., and Feinberg, L. J.: Glutamic Oxalacetic Transaminase in Chronic and Acute Peripheral Artery Occlusion. Clinical and Experimental Study. Am. J. Cardiol. **4**: 211 (Aug.), 1959.

The serum level of glutamic oxalacetic transaminase was found to be normal in 16 patients having chronic peripheral arterial insufficiency and in 16 of 19 patients who additionally had gangrene. The remaining 3 patients had elevated levels attributable to coincidental acute myocardial infarction or liver damage. In acute peripheral arterial occlusion, 7 of 9 patients had elevated transaminase levels 10 to 40 hours after symptomatic onset. Femoral artery ligation or embolization in dogs was regularly followed within 10 hours by rises in transaminase values to a peak of 340 units per ml. at 48 hours, and these returned to normal at about 130 hours.

ROGERS

Freedman, B. J., and Knowles, C. H. R.: Anterior Tibial Syndrome due to Arterial Embolism and Thrombosis. Brit. M. J. **2**: 270 (Aug. 29), 1959.

Five cases, 2 due to embolism and 3 to thrombosis, of the anterior tibial syndrome are described. The main clinical features were ischemic necrosis of the anterior tibialis muscle and, in greater or lesser degree, the extensor hallucis longus and extensor digitorum longus muscles. The immediate cause was occlusion of the anterior tibial artery or its parent trunk. This may be due to swelling of the muscles following unaccustomed exertion and resultant rise in intracompartmental pressure above the arterial blood pressure; local expanding lesions within the compartment, with similar effect; and embolism or thrombosis of the anterior tibial artery. For the postexertional cases a prompt incision to divide the deep fascia over the muscles is suggested to decompress the compartment. In cases due to

arterial thrombosis or embolism the use of vasodilating drugs and anticoagulation is indicated.

KRAUSE

Haimovici, H.: Late Arterial Embolectomy. Surgery **46**: 775 (Oct.), 1959.

The experience gained in 10 cases of late arterial embolectomy (carried out from 13 hours to 20 days after occlusion) is discussed. The results were good in 5. In 4, a degree of gangrene developed requiring amputation and 1 patient died with threatened gangrene. Preexisting vascular disease predisposed to recurrence of thrombosis at the site of the arteriotomy and also often precluded retrograde flushing. Pretreatment with anticoagulants in 6 patients seemed to account for the minimal or moderate secondary thrombosis encountered in those cases during embolectomy. In addition, anticoagulants seemed to prevent emboli and thrombi from adhering to the intima. A review of the literature is also presented.

SHEPS

Hines, E. A., Jr.: Diagnosis of Chronic Aorto-iliac Occlusive Arterial Disease. Ann. Int. Med. **51**: 679 (Oct.), 1959.

The most common symptom of arterial insufficiency is intermittent claudication, which is characterized by distress induced by exercise, usually walking, and is relieved within minutes by stopping and standing. It is important that a good history of the degree of limitation be obtained, and if there is any doubt, a standardized walking test should be performed. The physical examination in aorto-iliac occlusive arterial disease will usually reveal diminished or absent pulsations in the lower part of the abdominal aorta and below the bifurcation of the aorta. Coldness of the feet and legs, and pallor of the extremities on elevation are variable findings, depending upon the degree of collateral circulation. Aortography usually will visualize the site and degree of obstruction, and may reveal other sites of obstruction in the upper part of the femoral arteries and iliac arteries, if these are present. Aortography should be done only if the patient's symptoms are of sufficient severity to warrant surgical treatment and if the patient's age and general health will permit surgical treatment. Contraindications to angiography include bleeding disorders, anticoagulant therapy, and sensitivity to radiopaque substances. Since ischemic neuropathy, ischemic ulcers, or gangrene is uncommon in uncomplicated aorto-iliac occlusion, the author believes that surgical intervention must be individualized for each patient on the basis of symptoms of ischemia, and not routinely done in patients with evidence of occlusion of aorto-iliac arteries.

KAYDEN

Krause, R. J., Cranley, J. J., Baylon, L. M., and Strasser, E. S.: Two Recent Advancements in the Treatment of Peripheral Arterial Embolism. Arch. Surg. **79**: 285 (Aug.), 1959.

Experience in the management of 60 patients having 72 emboli is described. Forty-eight patients having 57 emboli were treated surgically and 7 patients having 9 emboli were treated by anticoagulant agents alone. Five patients were observed to whom no specific treatment was given. In 57 of the 60 patients, the heart was the site of origin of the embolus. Most of these patients had arteriosclerosis, a few had rheumatic fever, recent myocardial infarction and 1 had severe cardiac decompensation. Atrial fibrillation was present in 90 per cent of the patients. One patient had an abdominal aortic aneurysm and another a plastic valve in the proximal aorta, as the source for the embolus. In 1 patient no source was apparent. The technic of embolectomy is discussed, emphasizing the use of multiple arteriotomies and reversed flushing technics. The operative and postoperative use of anticoagulants is also emphasized. Heparin was used preoperatively to forestall propagation of a thrombus when a significant time lag between diagnosis and operation was unavoidable. The authors recommend permanent anticoagulant therapy after removal of an arterial embolus.

SHEPS

Mendlowitz, M., and Naftchi, N.: The Digital Circulation in Raynaud's Disease. Am. J. Cardiol. **4**: 580 (Nov.), 1959.

In 20 patients with Raynaud's disease, digital arterial pressure was measured with a Gaertner capsule and digital blood flow was measured calorimetrically under standardized conditions, after heat-induced vasodilatation and after *l*-norepinephrine-induced vasoconstriction. Eleven patients were found to have evidence of heightened vasomotor tone and no arterial obstruction; the remaining 9 displayed normal vasomotor tone and arterial obstruction. Only 1 patient showed increased sensitivity to norepinephrine. It was thought that Raynaud's attacks are produced either by arterial obstruction plus a normal degree of vasoconstriction tone or by heightened vasomotor tone alone, probably resulting from increased sympathetic neural discharge.

ROGERS

Pudwitz, K. R., and Reimers, H. F.: A Study of Cranial Vena Cava Occlusion of Unusual Origin. Ztschr. Kreislaufforsch. **48**: 951 (Oct.), 1959.

Occlusion of the cranial vena cava can be caused by malignant tumors, aortic aneurysms, mediastinal hemorrhage or emphysema, thrombophlebitis or thrombosis; the latter is rare. Gradual development of the obstruction allows adequate

formation of collateral vessels in the vicinity of the vertebral column and in the subcutaneous tissue of the chest wall. Three cases are presented in which the obstruction took place gradually and led to formation of subcutaneous varicosities without subjective symptoms. In 2 of these cases the obstruction could be shown by means of angiography, while in the third case a calcified thrombus could be seen during fluoroscopy and demonstrated at autopsy.

LEPESCHKIN

Riddell, D. H., Kirtley, J. A., Jr., Moore, J. L., and Goduco, R. S.: Scalenus Anticus Symptoms: Evaluation and Surgical Treatment. Surgery **47**: 115 (Jan.), 1960.

Experience in management of 53 patients with thoracic outlet compression symptoms treated by anterior scalenotomy is described. A few patients had adjunctive procedures such as excision of cervical rib, division of fibrous bands on ligaments and cervicodorsal sympathectomy. Of 42 patients who had evidence of nerve or artery compression, 80 per cent received relief of symptoms. Of 7 patients who had evidence of subclavian vein compression, 6 received relief of symptoms. The average duration of symptoms for the entire group was 27 months, but the average for 8 patients who had a persistence of symptoms was only 4 months. It was emphasized that careful preoperative evaluation and repeated examination are necessary to eliminate the more "undesirable candidates" for operation. Only in patients with objective signs are the operative results likely to be satisfactory. These signs include sensory loss, a supraclavicular mass, muscle atrophy, scalene tenderness, a cervical rib, the presence of Adson's sign, arterial insufficiency, and venous obstruction. A cervical rib was present in only 12 (22 per cent) patients. This condition must be differentiated from a ruptured nucleus pulposus of the cervical spine, cervical osteoarthritis, and the superior sulcus syndrome.

SHEPS

Sheranian, L. O., Edwards, J. E., and Kirklin, J. W.: Late Results in 110 Patients with Abdominal Aortic Aneurysms Treated by Resectional Replacement of Aortic Homograft. Surg., Gynec. & Obst. **109**: 309 (Sept.), 1959.

Of 135 patients having surgical exploration for abdominal aortic aneurysms during 1953 to 1957, 10 were found unsuitable for resection because of renal artery involvement and 15 had resection with replacement by a synthetic graft. The remaining 110 replacements were preserved homografts, 6 of which were inserted under emergency conditions. Eighteen patients died in the postoperative period, 8 from rupture of the graft or its suture lines; and 8 died 1½ to 2½ years later, 3 from graft failure. Because of homograft failure in these 11 patients, the authors currently use a cloth prosthesis. Eighty-one of the remaining patients have been traced over periods up to 4 years postoperatively, and their survival rates have been nearly the same as that of the normal population of the same age (63 years).

ROGERS

Smathers, H. M., and Smathers, W. M.: Carotid Artery Occlusion. Arch. Surg. **79**: 276 (Aug.), 1959.

The experience with surgery in 12 patients with carotid artery occlusion is summarized. Thromboendarterectomy was done in most patients. When the internal carotid artery is unusually small or extensively atherosclerotic, the authors suggest the prophylactic use of anticoagulants after surgery. Most favorable cases are those with intermittent symptoms with no paralysis at the time of surgery. It is doubtful that the patient with a paralysis of more than a few hours' duration can be helped surgically.

SHEPS

Troedsson, B. S.: Oscillometric Arterial Circulatory Norms. J. A. M. A. **172**: 141 (Jan. 9), 1960.

In obtaining objective "normal values" in peripheral arterial circulatory disorders several methods are currently used. Arteriograms have been most universally accepted but have the disadvantage of being surgical procedures. Evaluation with the oscillometer is gaining increasing recognition and the best known instrument for this method of testing is the Pachon type of mechanical oscillometer. Measurements were made in 12 healthy men and were used to calculate oscillometric indices at 6 levels from the instep of the foot to the upper part of the thigh. The interpretation of data was thus systematized so that an increasing number of patients (330 in 1958) could be evaluated for the medical and surgical services. The results of these oscillometric tests not only helped to determine the type of operation needed but also to serve as criteria for subsequent improvement in the patient. Two clinically useful norms were established by the use of a standardized oscillometer. The first norm is called the gangrene point and is expressed by an oscillometric index of zero at the instep, zero above the ankle, and 0.125 below the knee. The second norm can be called the walking norm or lower limit of normal and is represented by readings of 0.5 at the instep, 2.5 above the ankle, 4 below the knee, 3.5 above the knee, 2.5 in the middle of the thigh, and 2.5 in the upper part of the thigh. These norms have been used in 994 patients over a period of 4 years

and have been found to be reliable and useful. They provide an easy, practical method of objective evaluation and a permanent record for the physician.

KITCHELL

Wiedenmann, O., and Hipp, E.: Abnormal Communications between Branches of the Internal Carotid Artery and the Basilar Artery (Carotid-Basilar Anastomoses). Fortschr. Röntgenstr. 91: 350 (Sept.) 1959.

Of 7,382 carotid angiograms, carotid-basilar anastomoses were observed in 9 patients; in 6 persons a persistent primitive trigeminal artery was present, in 1 person a primitive acoustic artery, and in 2 individuals a primitive hypoglossal artery. This anastomosis can be easily recognized if during carotid angiography the posterior ramus communicans is not visualized but filling of the basilar artery takes place through a different, typically situated vessel. If the ramus communicans is also filled, the diagnosis is more difficult. The anastomoses usually do not cause any clinical symptoms.

LEPESCHKIN

OTHER SUBJECTS

Gordon, T., Moore, F. E., Shurtleff, D., and Dawber, T. R.: Some Methodologic Problems in the Long-term Study of Cardiovascular Disease: Observations on the Framingham Study. J. Chron. Dis. 10: 186 (Sept.), 1959.

A long-term surveillance of a closed population group in Framingham, Massachusetts, is discussed with relation to problems in the choice of populations for study and questions about the inferences that may be drawn from a survey approach. The progression of atherosclerotic and hypertensive heart disease in normal persons and in individuals with known disease has been followed. Some important characteristics studied in the epidemiology of coronary heart disease, such as relative weight, cholesterol, and blood pressure, are not altered permanently by the disease event. Relative weight, blood pressure, and cholesterol levels for men who develop new coronary heart disease are the same for those who die from the disease as for those who do not, but those women who died weighed less and had higher cholesterol levels than those who survived. There were biases reported in initial responses to the study and biases in follow-up by clinical and other means. The response rate differed by age and sex and according to the section of the town. It also differed according to certain clinical characteristics. This is inferred from a persistently higher mortality in the non-respondent group than in the respondent, and from differences between respondents re-examined regularly and those lost to follow-up. These biases are of moment in inferring from relationships shown by a description of the population but are considered trivial for prospective evaluation of hypotheses.

MAXWELL

REVIEWS IN CARDIOVASCULAR DISEASE

Raab, W.: Transmembrane Cationic Gradient and Blood Pressure Regulation. Interaction of Corticoids, Catecholamines and Electrolytes on Vascular Cells. Am. J. Cardiol. 4: 752 (Dec.), 1959.

Klemperer, P.: The History of Coronary Sclerosis. Am. J. Cardiol. 5: 94 (Jan.), 1960.

Koppel, J. L., and Olwin, J. H.: Physiologic Aspects of Intravascular Clotting. Am. J. Cardiol. 4: 585 (Nov.), 1959.

Bergofsky, E. H., Turino, G. M., and Fishman, A. P.: Cardiorespiratory Failure in Kyphoscoliosis. Medicine 38: 263 (Sept.), 1959.

Sciacca, A., and Condorelli, M.: Involution of the Ductus Arteriosus. Bibliotheca Cardiologica, Suppl. 10, 1960.

Nilsson, N. J.: Oximetry. Physiol. Rev. 40: 1, (Jan.), 1960.

Freis, E. D.: Hemodynamics of Hypertension. Physiol. Rev. 40: 27 (Jan.), 1960.

Dustan, H. P., Page, I. H., and Poutasse, E. F.: Renal Hypertension. New England J. Med. 261:647 (Sept. 24), 1959.

Nelson, J. R., and Smith, J. R.: The Pathologic Physiology of Pulmonary Embolism. A Physiologic Discussion of the Vascular Reactions Following Pulmonary Arterial Obstruction by Emboli of Varying Size. Am. Heart J. 58: 916 (Dec.), 1959.

Moller, B.: The Hydrogen Ion Concentration in Arterial Blood. Acta med. scandinav. suppl. 348, 1959.

Parker, R. G.: Occlusion of the Hepatic Veins in Man. Medicine 38: 369 (Dec.), 1959.

Brachfeld, N., and Gorlin, R.: Subaortic Stenosis: A Revised Concept of the Disease. Medicine 38: 415 (Dec.), 1959.

Koppel, J. L., and Olwin, J. H.: Physiologic Aspects of Intravascular Clotting. Am. J. Cardiol. 4: 585 (Nov.), 1959.

Huxley, H. E.: Muscular Contraction. Am. Heart J. 58: 777 (Nov.), 1959.

Dustan, H. P., Page, I. H., and Poutasse, E. F.: Renal Hypertension. New England J. Med. 261: 647 (Sept. 24), 1959.

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

Abstracts of Papers Due May 15 for 1961 AHA Scientific Sessions

Official application forms are now available for the submission of abstracts of papers to be presented at the Annual Scientific Sessions of the American Heart Association in Bal Harbour, Florida, October 20-22, 1961. *The deadline for submitting abstracts is May 15, 1961.*

Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must be limited to 250 words or less and include a brief digest of the results obtained and conclusions reached. All applications will be screened by the Committee on Scientific Sessions Program of the American Heart Association.

Official forms for submitting abstracts of papers may be obtained from Richard E. Hurley, M.D., Medical Associate, American Heart Association, 44 East 23rd Street, New York 10, New York. Applications for space for *scientific exhibits*, which must be returned postmarked not later than May 15, 1961, may also be obtained from Dr. Hurley.

Space for *industrial exhibits* may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, New York.

Epidemiology Conference Reports On Cardiovascular Diseases

The proceedings of a conference on "Epidemiology of Cardiovascular Diseases: Methodology—Hypertension and Arteriosclerosis," held in Princeton, New Jersey, April, 1959, under joint sponsorship of the American Heart Association and National Heart Institute, are now available as reprinted from the American Journal of Public Health.

Subjects considered include criteria for the diagnosis and clinical evaluation of ischemic heart disease and hypertension; dietary physical activity and biochemical measurements; assessment of cultural, societal, familial, psychological and genetic influences; and general problems of design of studies and analysis of data.

The 124-page report is obtainable at $1.00 a copy from the American Heart Association, 44 East 23rd Street, New York 10, New York.

New Lay Film, Leaflet Issued On Congestive Heart Failure

A new film, "Congestive Heart Failure," and an accompanying leaflet, "Facts About Congestive Heart Failure," have been issued by the Association for use by physicians in addressing lay audiences on this subject.

The film, through animated diagrams, reviews the work of the normal heart and circulatory system and explains what occurs during congestive failure. It discusses briefly the causes, symptoms and treatment of congestive failure and emphasizes that proper medical care can relieve or control the condition. Produced by Churchill-Wexler, the 16mm color and sound film runs for eight and one-quarter minutes. It may be rented or purchased from the AHA Film Library, 267 West 25th Street, New York 1, New York.

The leaflet may also be useful to physicians for educating patients and their families. It is available without cost from the American Heart Association or its local affiliates.

Cardiac Work Evaluation Units Conference Report Ready

Proceedings of the Second National Conference on Work Evaluation Units for cardiac patients, sponsored by the Association last May in Harriman, New York, are available without cost from the National Office or local Heart Associations.

The 70-page report covers current purposes, research potentials, recommended practices and the future of such evaluation units. The conference was attended by cardiologists, internists, psychiatrists, psychologists, social workers, rehabilitation counselors and representatives of Government employment and rehabilitation agencies.

AHA Professional Materials Listed

The Association's catalog, "Publications and Visual Aids for Physicians," which describes all professional materials produced by the American Heart Association, has been revised and brought up to date. Copies may be obtained free of charge from the Association or its local affiliates and chapters.

Scripts of Lay Films Available

Scripts of the Association's films for lay audiences on the subjects of "Stroke," "Coronary Heart Disease" and "Congenital Heart Defects," are now available to physicians through the AHA National Office or local Heart Associations. These are intended to acquaint the physician with the film's contents when time does not permit its review in advance of the initial showing.

Diagnostic Radiology Society

Applications for charter membership are now being received by the American Society for Diagnostic Radiology from physicians interested in doing some types of diagnostic radiology in their offices. Information may be obtained from Louis Shattuck Baer, M.D., F.A.C.P., 411 Primrose Road, Burlingame, California.

1961 Subscription Renewals

Renewals of subscriptions for 1961 of *Circulation* and *Circulation Research*, official journals published by the Association, should be made through the Publishing Office, American Heart Association, 44 East 23rd Street, New York 10, New York. Annual Subscription rates are: *Circulation* (12 issues) $14 in the U.S. and Canada, $15 elsewhere. *Circulation Research* (6 issues), $9 in the U.S. and Canada, $10 elsewhere. (Special annual rate for full-time research fellows, *Circulation Research* only $7.) Combined subscriptions to both journals, $21 in the U.S. and Canada, $23 elsewhere. Special rate for interns, residents and medical students, U.S. and Canada, only, *Circulation* $9; *Circulation Research* $6.

Meetings Calendar

February 8-11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Dr., Chicago 6, Illinois.

February 9-11: Society of University Surgeons, Kansas City, Kansas. B. Eiseman, 4200 E. 9th Ave., Denver, Colorado.

February 16-18: Central Surgical Association, St. Louis. A. D. McLachlin, Victoria Hospital, London, Ontario, Canada.

March 6-9: American College of Surgeons, Sectional Meeting, Philadelphia. William E. Adams, 40 E. Erie St., Chicago 11, Illinois.

March 13-16: National Health Council, New York. Philip E. Ryan, 1790 Broadway, New York 19, New York.

March 20-24: American Surgical Association, Boca Raton, Florida. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 10-14: American Physiological Society, Atlantic City. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D.C.

April 17-20: American Academy of General Practice, Miami Beach. Mae F. Cahal, Volker at Brookside, Kansas City 12, Missouri.

April 24-26: American Association for Thoracic Surgery, Philadelphia. Miss Ada Harvey, 7730 Carondelet Ave., St. Louis 5, Missouri.

April 28-30: American Psychosomatic Society,

Atlantic City. Morton F. Reiser, 265 Nassau Rd., Roosevelt, New York.

April 30: American Federation for Clinical Research, Atlantic City. James E. Bryan, 250 W. 57th St., New York 19, New York.

May 2-3: Association of American Physicians, Atlantic City. Paul Beeson, Yale University School of Medicine, New Haven 11, Connecticut.

May 5-7: American Society of Internal Medicine, Miami Beach, G. T. Bates, 350 Post St., San Francisco 8, California.

May 8-12: American College of Physicians, Miami Beach. E. C. Rosenow, Jr., 4200 Pine St., Philadelphia 4, Pennsylvania.

May 16-20: American College of Cardiology, New York. Philip Reichert, 350 Fifth Ave., New York 1, New York.

May 31-June 2: Canadian Federation of Biological Societies, Ontario. E. H. Bensley, 1650 Cedar Ave., Montreal 25, Canada.

June 22-26: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Illinois.

June 25: Society for Vascular Surgery, New York. George H. Yeager, 314 Medical Arts Bldg., Baltimore 1, Maryland.

June 26-30: American Medical Association, Annual Meeting, New York. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

July 1-4: International College of Surgeons, New England Regional Meeting, Cape Cod, Massachusetts. M. L. Brodny, 4646 N. Marine Dr., Chicago 40, Illinois.

August 27-September 1: American Congress of Physical Medicine and Rehabilitation, Cleveland. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Illinois.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

Abroad

March 17-19: International Medical Conference, Liege, Belgium. Secretariat, Castellezgasse 35, Vienna 11, Austria.

June 2-5: Latin-American Congress of Physical Medicine, Lisbon. C. L. deVictoria, 245 E. 17th St., New York, New York.

June 3-15: International Medical-Surgical Meetings, Turin, Italy. Minerva Medica, Corso Bramante 85, Turin.

August 22-25: International Pharmacological Meeting (First), Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

September 3-10: Inter-American Congress of Radiology, Sao Paulo. W. Bomfim-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

September 6-12: International Congress of Human Genetics, Rome. Luigi Gedda, 5 Piazza Galeno, Rome, Italy.

September 10-15: International Neurological Congress, Rome. G. Alema, Viale Universita, 30 Rome, Italy.

September 18-22: International Congress of Neuroradiology, Rome. E. Valentino, Piazza Colonna 193, Rome, Italy.

1962

October: Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc 300, Mexico, D.F.

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